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THE USE OF PROTAMINE ZINC INSULIN IN DIABETIC COMA*

BY I. M. RABINOWITCH, A. F. FOWLER AND E. H. BENSLEY

Montreal

IN previous communications from this Clinic^{1, 2} it was shown that protamine zinc insulin (Scott and Fisher) is a more effective agent for the control of diabetes than protamine insulin (Hagedorn). It was found to be equally effective in a variety of types of diabetes, with and without infection, and with and without acidosis. A number of other workers have since reported their experiences with protamine zinc insulin, and, though difficulties have been met with, there is general agreement that the addition of zinc to Hagedorn's protamine insulin represents a definite advance in the treatment of diabetes mellitus. Wilder and Wilbur, of the Mayo Clinic, have pointed out³ that even in their difficult cases, in spite of the intermittent glycosuria which it was necessary to maintain in order to avoid hypoglycæmic reactions, the patients seemed to feel healthier and stronger than before. This is in accord with our own experiences.

In one of the above-mentioned reports² it was shown that, in spite of the binding effects of protamine and zinc, it is possible to decrease the concentration of sugar in the blood with a single injection of protamine zinc insulin as rapidly as with unmodified insulin, providing the dosage is large. This alone suggests that protamine zinc insulin is not contraindicated in conditions where rapid action is necessary. Proof of its reliability in such cases was shown later in our experiences with surgical diabetics.⁴ In fact, Tables III, IV and V of the latter report show that because of its prolonged action the protamine zinc insulin was more effective than the unmodified insulin, when consideration

was given to the surgical condition, type of operation, and type and duration of the anæsthetic. The only remaining condition, therefore, in which it is necessary to test the effectiveness of protamine zinc insulin is the last stage of uncontrolled diabetes, that is, diabetic coma.

Diabetic coma is now very uncommon; in 1936 there were only three cases in this Clinic. Because of an undue prevalence of influenza recently, however, a number of diabetics were admitted within a very short time to the wards of the Montreal General Hospital in various stages of coma, and the purpose of this communication is to report the results obtained in their treatment. *The data clearly show that protamine zinc insulin is not only not contraindicated in coma but is ideal.* With the unmodified insulin, as is well known, frequent injections (at times hourly) are invariably necessary in severe cases. Frequent injections are also necessary as a rule during the following 24 or 48 hours, in spite of the small amounts of food which patients can be made to take. By the method to be described, it will be shown that even in very severe cases *one* simultaneous injection of unmodified insulin and protamine zinc insulin led to rapid reduction of the blood sugar to the normal level and rapid recovery. No more injections were necessary to keep the blood sugar normal for periods which ranged between 38 and 62 hours, in spite of administration of amounts of carbohydrate from 780 to 1,020 grams. Diabetic coma almost invariably causes some damage to the kidneys, but it will be shown that practically all of these large amounts of carbohydrate were properly utilized—either by oxidation or storage—and not merely retained in the body, because of failure of renal excretion.

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NOMENCLATURE

Lawrence and Archer⁵ have recently pointed out the necessity for a universally accepted code of nomenclature with respect to the different preparations of protamine, zinc and insulin. That there is such a necessity is obvious from any attempt to compare the data of different workers. A difficulty with the earlier work was failure to record the concentrations of zinc and protamine in the different preparations used. That the action of insulin may be influenced to a very appreciable extent by its content of zinc was definitely demonstrated by Scott and Fisher in the Connaught Laboratories in animals⁶ and in this Clinic in man.¹ In the latter report, we also showed by spectrographic analyses that the different preparations used in the past varied widely with respect to their zinc contents. The protamine zinc insulin now in general use is a standardized product. There is still, however, much confusion owing to the practice of referring to protamine insulin and protamine zinc insulin as though the two products were identical in action. The two cases of coma described by Kepler, Ingham and Crisler,⁷ for example, were treated with protamine zinc insulin and not with protamine insulin as reported (personal communication). In the latest edition of his "Treatment of Diabetes Mellitus", Joslin⁸ also uses the two names synonymously. On page 323, for example, Rabinowitch, Fowler and Corcoran are credited with the observation that carbohydrate tolerance was improved in 15 out of 31 cases treated with protamine insulin. They are also credited with the observation that a single injection of protamine insulin lowered the blood sugar from 0.270 to 0.147 per cent in a case of gangrene with acidosis. The actual reports of these cases, however,² clearly state that the product used was *protamine zinc insulin* and not protamine insulin. That the terms are used interchangeably is definitely shown in a footnote on page 314, where it is stated that, in general, throughout the book when the words protamine insulin are used they refer to protamine zinc insulin. In order, therefore, to avoid further confusion, it is necessary to state that the results in the cases of coma to be reported here were obtained with the *protamine zinc insulin* (Scott and Fisher) which contains 1 mg. of zinc per 500 units of insulin.

THE PREVIOUS USE OF PROTAMINE ZINC INSULIN IN COMA

Up to March, 1937, with an experience of more than 1,000 cases, Joslin⁸ does not include coma under "Indications for use of protamine insulin". Wilder and Wilbur³ reported successful control of the severe acidosis in one case by a single injection of 75 units of protamine insulin. Nothing was reported, however, to suggest coma or pre-coma other than the low CO₂ combining power of the blood plasma (17 volumes per cent). In the above-mentioned report of Kepler, Ingham and Crisler⁷ there is the statement that, "to date, four patients, with severe diabetic acidosis, have been treated successfully at the Clinic with regular insulin supplemented by protamine insulin. Two of these patients were in profound coma." The data of these two cases, however, clearly show that protamine insulin played practically no part in one case and very little in the other in the immediate recovery of these patients. In Case 1 the patient had received eight injections (approximately 200 units) of unmodified insulin and the blood sugar was reduced to the normal level before the protamine insulin was administered. In the other case, of the 725 units which were administered in 13 injections during the first 24 hours protamine insulin accounted for one injection of 50 units only. In the summary of the experiences with their four cases these authors advise *against* the use of protamine insulin in diabetic acidosis of any marked degree of severity, since "every moment counts and vigorous treatment with the rapidly acting regular insulin is, in most cases, imperative". Lawrence and Archer⁵ state that "zinc protamine insulin is very useful in the treatment of diabetic coma", but give no data.

That protamine zinc insulin may be effective in coma was first suggested from our previously reported¹ experiences with a child 5 years old. This, however, was a case of pre-coma only. Juvenile diabetics also, as a rule, respond more readily to insulin than adults. The very satisfactory recovery with the small amount of protamine zinc insulin used alone suggests that this was not a satisfactory test case. Subsequent experiences with an adult were more suggestive.⁴ Though this also was a case of pre-coma, the diabetes was complicated by a severe infection. In this case (Hosp. No. 159/37) in spite of a

carbuncle, the blood sugar was reduced from 0.256 to 0.137 per cent in three hours.

The problem of determining the applicability of protamine zinc insulin in coma was not simple. With two exceptions only, the coma was complicated in all of our cases by infection and, as is well known, such patients may at times fail to respond even to very large doses of unmodified insulin. Occasionally, also, the immediate response to unmodified insulin may be an increase, instead of a decrease, of the blood sugar; there may be an appreciable lag between the time of injection and the beginning of the lowering of the blood sugar and, at times, the reduction of blood sugar, though progressive, may be very slow. All of these reactions have also been noted in our experiences with protamine zinc insulin. This is shown in Table I. It will be noted that the immediate response in Case 1 was an increase instead of a reduction of the blood sugar. It is of interest to note that the same phenomenon was observed by

Kepler, Ingham and Crisler⁷ in one of their cases, in spite of five previous injections of unmodified insulin.

Case 4 in Table I is very instructive. The data very clearly demonstrate that failure to lower the blood sugar rapidly with protamine zinc insulin is not to be attributed invariably to the binding action of the zinc and protamine. It will be noted that the injection of the protamine zinc insulin was followed by a progressive but gradual reduction of the blood sugar. That the slow effect was not due to any property peculiar to protamine zinc insulin but to the metabolic state of the patient is, however, clearly shown by the failure to lower the blood sugar any more rapidly with repeated injections of equally large amounts of unmodified insulin intravenously.

THE BASIS OF THE METHOD OF USING PROTAMINE ZINC INSULIN IN COMA

In the attempt to find the most effective

TABLE I.
SHOWING DIFFERENT RESPONSES TO LARGE SINGLE INJECTIONS OF
PROTAMINE ZINC INSULIN IN DIABETIC COMA

No.	Hospital No.	Sex	Age	Hour	Blood sugar (per cent)	Insulin		Response
						Type	Units	
1	5786/36	F	24	2.30 p.m. 3.30 " 4.30 "	0.526 0.666 0.512	PZI*	100	Increase of blood sugar one hour after injection followed by a decrease.
2	1515/37	M	28	5.30 " 6.30 " 7.30 " 8.30 " 9.10 "	0.385 0.370 0.370 0.256 0.216	PZI	400	Slight decrease of blood sugar followed by a lag, then rapid decline.
3	1331/37	F	64	5.00 " 6.00 " 7.00 " 8.00 " 9.00 "	0.416 0.344 0.285 0.285 0.277	PZI	200	Rapid decrease of blood sugar followed by a lag.
4	5304/36	M	22	4.40 " 6.40 " 8.40 " 11.30 " 12.30 a.m. 1.00 " 2.00 " 3.00 " 4.00 " 5.00 " 6.00 " 7.00 " 8.00 " 9.00 "	0.500 0.434 0.400 0.362 0.333 0.302 0.285 0.270 0.217 0.208 0.181 0.128 0.100	PZI UMI† UMI PZI UMI UMI UMI	100 150‡ 100 100 100 50 50	Progressive, but slow, decrease of blood sugar not influenced by subsequently repeated injections of unmodified insulin intravenously.

*PZI—Protamine zinc insulin.

†UMI—Unmodified insulin.

‡25 units at 9.40 p.m.; 25 units at 10.05 p.m., and 100 units at 11.05 p.m.

method of using protamine zinc insulin in coma consideration was given to a number of conditions which may influence the utilization of carbohydrates. Himsworth, for example, in a series of publications^{9 to 13} demonstrated very convincingly that carbohydrates improve, whereas fats impair, carbohydrate tolerance, and that carbohydrates increase, whereas fats decrease, the sensitivity of the individual, animal or man, to injected insulin. Ellis¹⁴ demonstrated rapid and marked improvement of carbohydrate tolerance in severe diabetics by hourly administration of glucose and insulin. In one case the daily dosage of insulin was reduced from 192 to 9 units after 21 days of such treatment. The findings of these workers fit in with and probably explain the improvements of carbohydrate tolerance which we have observed in our own cases¹⁵ and the satisfactory results in general with the high carbohydrate-low calorie diets.^{16 to 19} The combined data, therefore, suggest that proper treatment of diabetic coma should consist not only of adequate insulin dosage to lower the blood sugar to the normal level but of adequate dosage to permit administration of large amounts of carbohydrate. Himsworth has had this idea for some time.⁹

There are a number of factors to consider with regard to insulin *per se*. As stated, protamine zinc insulin may be made to act as rapidly as subcutaneous injections of unmodified insulin.² At times, however, especially in coma, still more

rapid action may be necessary. An important fact, therefore, is that insulin acts much more rapidly when injected directly into the blood stream. Unfortunately, protamine zinc insulin is a suspension and not a solution. It was, therefore, doubtful whether it could be administered intravenously with safety. An advantage of protamine zinc insulin, however, is its prolonged action. We have also shown² that, providing the dosage of protamine zinc insulin is large, a further increase of dosage does not increase the rate at which the blood sugar may be made to decrease; there is little or no summation of effect. Combining all of these observations, it appeared that, instead of the frequent administration of unmodified insulin, it should be possible with *one simultaneous injection of unmodified insulin intravenously and unmodified and protamine zinc insulin subcutaneously* not only to lower the blood sugar rapidly to the normal level but to keep it at the normal level for many hours, in spite of administration of large amounts of carbohydrates.

The first indication that the above method of treatment was possible was met with in the case shown in Chart 1 (Hosp. No. 964/37). The coma was very severe* and was precipitated by an acute upper respiratory infection. The progress in general appeared to be poor, and for this reason the patient was given a very large

* For criteria of severity see Estimation of Severity of Coma and Prognosis (page 110).

BLOOD SUGAR TIME CURVES IN 3 CASES OF DIABETIC COMA FOLLOWING SIMULTANEOUS ADMINISTRATION OF UNMODIFIED INSULIN AND PROTAMINE ZINC INSULIN SHOWING RAPID REDUCTION OF THE BLOOD SUGAR AND PROLONGATION OF THE ACTION OF THE INSULIN IN SPITE OF FREQUENT ADMINISTRATION OF CARBOHYDRATES.

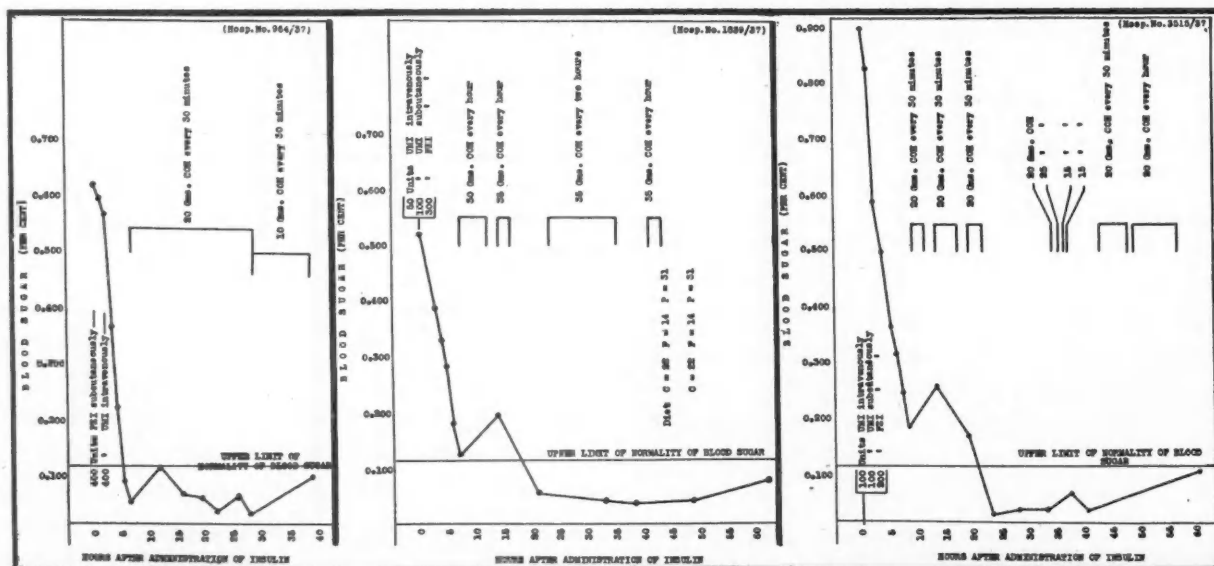


Chart 1

Chart 2

Chart 3

dose (400 units) of protamine zinc insulin at one injection as soon as the blood had been collected for examination. Two hours later he was given 400 units of unmodified insulin intravenously. The subsequent blood sugar values are graphically recorded in Chart 1. It will be noted that the blood sugar was rapidly reduced to the normal level and maintained at that level *in spite of the administration of over one thousand grams of carbohydrate during a period of 32 hours*. The recovery clinically paralleled the laboratory findings. The relationship between the amount of carbohydrates given and the amount utilized by the body will be dealt with under "carbohydrate balances".

To put the suggested method to more tests, it was necessary to await the admission of patients with equally, or approximately equally, severe forms of coma, and in Charts 2 and 3 are graphically recorded the results obtained in two other cases. Both showed signs of circulatory failure; the systolic blood pressures were below 100 mm. Hg. Some idea of the degrees of toxicity may also be gained from the amount of kidney damage. As is usual in coma²⁰ the urine in each case contained albumin and a shower of casts, but the blood also showed definite nitrogen retention. Appreciable nitrogen retention, as is well known, does not occur as a rule unless the coma is severe or of long duration. That the nitrogen retention in each of these cases was due to damage of the kidneys by the severity of the coma and not to a previously existent advanced chronic nephritis is shown by the reduction of the urea nitrogen to the normal level three days after the recovery from the coma. Thus:

Case No.	Urea Nitrogen (mg. per 100 c.c. blood)	
	On admission	3 days later
3515/37	48	11
1839/37	50	14

The data in the above charts require very little comment. It will be noted that in each case treatment consisted of *one* simultaneous injection of unmodified insulin intravenously, unmodified insulin subcutaneously, and protamine zinc insulin subcutaneously, and in both cases the response was practically the same; the blood sugar was rapidly reduced to the normal

level, and was still at the normal level 60 hours later in Case 2 and 62 hours later in Case 3.

CARBOHYDRATE BALANCES

In Table II are recorded the carbohydrate balances to show the amounts of carbohydrate ingested and excreted during the periods of feeding. It will be noted in each case that practically all of the carbohydrate administered

TABLE II.
CARBOHYDRATE BALANCES
(Showing relationship between intake and urinary excretion of sugar)

	Subject	964/37	1839/37	3515/37
	*Period	32	48.5	43
Balance	Intake (gm.)	1020	780	835
	Excreted (gm.)	10	32	63
	†Utilized (gm.)	1010	748	772

*Number of hours during which total amount of sugar was administered.

†The normal blood sugar at the end of each period of observation excludes artificial accumulation in the body due to impairment of kidney function; it definitely indicates that the amount of carbohydrate retained represented the amount completely utilized either by oxidation or storage or both.

was retained. Without blood sugar estimations, however, these data would be of limited significance, because of the severe kidney damage. The incontestable proof that the large amount of carbohydrate retained in each case was properly utilized either by oxidation or storage, or both, is the fact that the blood sugar was perfectly normal at the end of the period of observation; the absence of hyperglycemia definitely excludes artificial accumulations. So far as could be ascertained from the literature such degrees of utilization of carbohydrates as shown here had never been observed hitherto in diabetic coma. It should also be noted that, in addition to the utilization of these large amounts of carbohydrate, it was also necessary for the injected insulin to control the hyperglycemia and glycosuria prior to their administration.

It is a well known fact that the blood sugar may return to the normal level in coma before the patient has fully recovered clinically. It should, therefore, be observed that the clinical course in each case paralleled the laboratory findings, and of special interest, and fitting in with the clinical picture, was the rapid disappearance of the acetone bodies from the

breath and urine. Such rapid disappearances have been noted before with frequent injections of unmodified insulin. The same occurrence in three consecutive cases is, however, very suggestive. The findings fit in with a very active carbohydrate metabolism.

THE DANGERS OF OVERDOSAGE WITH INSULIN

A severe insulin hypoglycæmic reaction is a possibility which must be considered with the above-mentioned method of treatment. The dangers, however, as will presently be shown, are largely theoretical.

The diabetic in coma is dying of a condition which is due essentially to lack of insulin. Regardless of any other therapeutic measures—alkalis, control of dehydration, etc.—before the discovery of insulin, every diabetic in coma died. Joslin⁸ states that he has “never seen hypoglycæmia following recovery from diabetic coma which gave rise to or resulted in any serious difficulty”, and as far as could be ascertained from the literature, there is, as yet, no recorded death from an overdosage of insulin *during treatment* of coma. In fact, when consideration is given to the large number of patients who require relatively large amounts of insulin, deaths from overdosage are very rare even in healthy diabetics. The treatment of diabetic coma in this Clinic during the past few years has been upon this fact and the results have been very gratifying. Our records show that amongst the last twelve cases of coma, the average dosage of insulin *at the first injection* was 192 units, and it is to this large dosage that we attribute the fact that there have been no deaths, in spite of the fact that two only of these patients were free of complications. All of the remaining cases were complicated by infection, a condition known to interfere with the action of insulin; 6 had upper respiratory infections (influenza?); 1 had bronchopneumonia; 1 had an abscess; there was 1 case of carbuncle and 1 of gangrene.* In four other cases of coma observed during this period the initial dosages were 150, 200, 300 and 300 units, respectively. All of these patients also recovered. They are, however, not included in

* A recent death is not included, since the patient was admitted in a moribund condition and died shortly after, before there was an opportunity to institute any measures other than the injection of insulin.

the above list, since they were seen in consultation only outside of the hospital by one of the writers (I.M.R.). The population statistics of the Clinic for Diabetes of this hospital include only patients admitted to the public indoor and outdoor and private indoor and outdoor services of the hospital.

ESTIMATION OF INSULIN DOSAGE

Not all cases of coma are of equal severity. It is, therefore, necessary to grade the amounts of insulin. From our experiences to date, the frequent (hourly or half-hourly) administration of sugar in some form should, alone, prevent severe hypoglycæmic reactions. The following dosages, however, appear to be sufficiently low to avoid even mild disturbances.

Degree of coma	Unmodified insulin* (subcutaneously)	Treatment Unmodified insulin (intravenously)	Protamine zinc insulin* (subcutaneously)
Mild	25	25	50
Moderate ..	50	50	100
Severe	75	75	150
Profound ..	100	100	200

* Lawrence and Archer⁵ found that unmodified insulin and protamine zinc insulin could be mixed in one syringe, injected together and yet retain their separate properties. This has not been our experience. To obtain the best results we have found it necessary to administer unmodified insulin and protamine zinc insulin in separate syringes, with separate needles, and in separate parts of the body.

With large doses, it is also our practice to inject the suspension at 3 or 4 different sites of the body not only to avoid the discomfort of distension of the tissues due to bulk but also to insure more rapid absorption.

ESTIMATION OF THE SEVERITY OF COMA AND THE PROGNOSIS

To be of any value outside of hospital practice the method of estimating the severity of the coma in any given case must be clinical. Fortunately, the clinical method is the most reliable. It should be observed that all of the laboratory tests—quantitative estimation of acetone bodies, urinary ammonia, alveolar CO₂, CO₂ combining power of the blood plasma, etc.—merely afford an indication of the degree of acidosis. Diabetic coma, however, though precipitated by acidosis, is a much more complicated condition. Proof of this lies in the many vagaries of the CO₂ combining power of the blood plasma.

Careful correlation of the clinical and laboratory data for many years has taught us that this test is practically of little or no value in the majority of cases, and where it does reflect the severity of the acidosis it is accompanied by other and more simple signs. We have seen diabetics deeply unconscious with CO_2 values of 15 volumes per cent and more, and drowsy or semi-conscious only with values as little as 5 volumes per cent. Nor does the CO_2 combining power of the blood plasma indicate the prognosis. That we are not alone in this experience is obvious from the reports of other workers. In the latest edition of his book, for example, Joslin,⁸ though he still uses this test as a routine, records the fact that of 36 patients with 5 volumes per cent or less, 30 recovered, and of 10 with the extremely low value of 2 volumes per cent, 8 recovered. Further, of 41 fatal cases, the CO_2 combining power of the blood plasma was 15 volumes per cent or more.

CLINICAL CRITERIA

To be of any value in the estimation of the severity of the coma and in prognosis, the clinical examination must be thorough and includes a variety of observations.

Age.—Young people respond more readily to insulin than elderly individuals. They, therefore, require less insulin than elderly people for the same degree of coma.

Duration of the coma.—The response to insulin decreases with the duration of the coma. For the same degree of coma, the longer the duration, the larger should be the insulin dosage.

Degree of coma.—Ordinarily, the coma may be regarded as mild when there is drowsiness only; moderately severe, when the individual is semi-conscious; severe, when there is unconsciousness, but there is still response to pain; and very severe, when there is complete unconsciousness.

Complications.—The above rule becomes entirely unreliable as an index of insulin dosage in the presence of complications. With an infection, for example, the prognosis with drowsiness only may be much more grave and the insulin requirements much greater than with complete unconsciousness without infection. Any condition which, *per se*, may cause hyperglycemia, may also interfere with the action of the injected insulin and thus require larger dosages.

Condition of the circulation.—With mild coma, the pulse, though rapid, is full and bounding. The blood pressure is normal or increased, and the skin is warm, dry and has a good colour. As the coma becomes more and more severe, the pulse increases in rate, but decreases in volume. The blood pressure decreases; the skin then loses its healthy appearance; its temperature decreases and it becomes moist. Sweating, it should be observed, is uncommon in mild uncomplicated coma. When present, it is generally due to the shock of severe diabetic intoxication or some complication and is generally associated with a low blood pressure; with extremely few exceptions a systolic blood pressure of less than 90 mm. hg. invariably indicates severe coma.

Disappearance of Kussmaul respirations.—Replacement of the usually expected deep, laboured, pauseless breathing by feeble, gasping respirations indicates that the patient is approaching the last stages of coma. The dosage of insulin should always be large at this time, but without other measures to combat respiratory and circulatory failure this alone will be futile.

Urine volume output.—Dehydration of the body due to previous polyuria or vomiting may *per se* decrease the output of urine and interfere with excretion of the ketone bodies. The prognosis is, however, not as grave as with anuria due to circulatory failure or coma of long duration.

Coffee grounds vomitus.—This indicates severe intoxication regardless of the degree of unconsciousness.

Laboratory tests.—These are not available in ordinary practice. They are, therefore, not included as an index of the severity of the coma or prognosis.

Response to treatment.—The best indication of severity and prognosis is the immediate response to treatment. If the coma has been established as mild, but the response to the corresponding dosage has not been satisfactory at the end of one hour, there should be no hesitation whatever about increasing the dosage. *It cannot be emphasized too often that the immediate danger of death in coma is not overdosage, but lack of insulin.*

Parenthetically, it should be observed that the above method of treatment does not exclude the necessity of the usual procedures otherwise which depend upon the degree of coma—application of heat to the body, enemata, isotonic sodium chloride solutions to combat dehydration, hypertonic sodium chloride solutions to combat anuria, stimulants for circulatory or respiratory collapse, etc.

SUMMARY

An attempt was made to treat coma on the basis of (a) the differences of action of unmodified insulin when administered intravenously and subcutaneously; (b) the known differences between unmodified insulin and protamine zinc insulin; and (c) the experimental results with respect to the influence of carbohydrates and fats upon the action of insulin in general.

The treatment consisted of one simultaneous administration of unmodified insulin intravenously, unmodified insulin subcutaneously and protamine zinc insulin subcutaneously in large amounts, followed by the frequent administration of carbohydrates.

Cases are presented to show that with the above method of treatment the blood sugar may be lowered very rapidly to the normal level, even in very severe coma, and maintained at that level for many hours in spite of the administration of many hundreds of grams of carbohydrate.

Data are presented to show that the retention of the large amounts of carbohydrate administered in these cases was not due to inability on the part of the kidneys to excrete the sugar but to proper utilization by oxidation or storage, or both.

This work was done, and is being continued, with the aid of a grant from Mr. J. C. Newman, Vice-president, Mr. Julian C. Smith, member of the Board of Management, and Mr. W. S. Fallis, Governor, of the Montreal General Hospital.

REFERENCES

1. RABINOWITCH, I. M., FOSTER, J. S., FOWLER, A. F. AND CORCORAN, A. C.: Clinical experiences with protamine zinc insulin and other mixtures of zinc and insulin in diabetes mellitus, *Canad. M. Ass. J.*, 1936, 35: 239.
2. RABINOWITCH, I. M., FOWLER, A. F. AND CORCORAN, A. C.: Further observations on the use of protamine zinc insulin in diabetes mellitus, *Canad. M. Ass. J.*, 1937, 36: 111.
3. WILDER, R. M. AND WILBUR, D. L.: Diseases of metabolism and nutrition, *Arch. Int. Med.*, 1937, 59: 329.
4. FOWLER, A. F., BENSLEY, E. H. AND RABINOWITCH, I. M.: Control of diabetes mellitus with protamine zinc insulin in surgery, *Canad. M. Ass. J.*, 1937, 36: 561.
5. LAWRENCE, R. D. AND ARCHER, N.: Zinc protamine insulin, *Brit. M. J.*, 1937, 1: 487.
6. SCOTT, D. A. AND FISHER, A. M.: The prolongation of insulin action by protamine and zinc, *Proc. Am. Soc. Biol. Chem.*, 1936, 88: 8.
7. KEPLER, E. J., INGHAM, D. W. AND CRISLER, G. R.: Protamine insulin as an adjunct to the treatment of diabetic acidosis and coma, *Proc. Mayo Clinic*, 1937, 12: 171.
8. JOSLIN, E. P.: Treatment of Diabetes Mellitus, 6th ed., Lea and Febiger, Phila., 1937.
9. HIMSWORTH, H. P.: The rôle of glucose in the treatment of diabetic intoxication, *The Lancet*, 1932, 2: 165.
10. *Ibid.*: The physiological activation of insulin, *Clin. Science*, 1933, 1: 1.
11. *Ibid.*: High carbohydrate diets and insulin efficiency, *Brit. M. J.*, 1934, 2: 57.
12. *Ibid.*: Dietetic factors influencing glucose tolerance and activity of insulin, *J. Physiol.*, 1934, 81: 29.
13. *Ibid.*: The dietetic factor in glucose tolerance, etc., *Clin. Science*, 1935, 2: 67.
14. ELLIS, A.: Increased carbohydrate tolerance in diabetes following the hourly administration of glucose and insulin, *Quart. J. Med.*, 1934, 3: 137.
15. RABINOWITCH, I. M.: Effects of high carbohydrate-low calorie diet, etc., *Canad. M. Ass. J.*, 1935, 33: 136.
16. *Ibid.*: Experiences with a high carbohydrate-low calorie diet, etc., *Canad. M. Ass. J.*, 1930, 23: 489.
17. *Ibid.*: Clinical and laboratory experiences with high carbohydrate-low calorie diets, etc., *New Eng. J. Med.*, 1931, 16: 799.
18. *Ibid.*: The present status of the high carbohydrate-low calorie diets, etc., *Canad. M. Ass. J.*, 1932, 26: 141.
19. *Ibid.*: Observations on the cholesterol content of blood plasma, etc., *Canad. M. Ass. J.*, 1933, 28: 162.
20. *Ibid.*: The kidneys in diabetic coma, *Canad. M. Ass. J.*, 1929, 21: 274.

THE RELATION BETWEEN HORMONES AND CANCER*

BY ANTOINE LACASSAGNE, M.D.

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TO appreciate fairly the state of the cancer problem, one must defend himself against two tendencies of judgment which are very current. On the one hand are the sceptics for whom this affection constitutes a mysterious domain, closed to all penetration of knowledge; on the other hand are those of imagination to whom each new biological fact brings arguments to verbally explain all. In reality, cancer is one of the diseases which has received the most benefit from the development of experimental research, which, in turn, has established the peculiar complexity of this object of study.

By all hypotheses the mechanism of the cellular disease—by which a normal element becomes a cancerous element—remains unknown. But considerable progress has been realized in the knowledge of agents susceptible of provoking this cytological change. It seems likely that these are multiple and very different one from the other, since cancerization follows as the end-result of an alteration which can be

accomplished, in the same cell, by agents so dissimilar as radiation, chemical substances, and perhaps microorganisms. This is why, if one is permitted to speak today of certain relations between the hormones and cancer, it must be well understood that this concerns a pathogenesis valid for certain neoplasms only and under very particular conditions.

The unfolding of the rôle, which is becoming ever more important, of hormones in regard to growth in general and in the development of certain systems of organs, impels the thought that a similar link could equally subordinate tumoural multiplication to the local or general influences of chemical agents of growth. To sustain this point of view numerous arguments derived from general pathology or even from the clinic could be offered, to afford material for debate. But, in holding to experimental facts, one must admit that of the principal growth hormones actually demonstrated (hypophyseal, gonadal, thyroid and cortico-suprarenal) only the first two have up to the present furnished very convincing indications (ap-

* Read at the Sixty-eighth Annual Meeting of the Canadian Medical Association, Ottawa, June 24, 1937.

proaching proof) in favour of a correlation of certain cancers with them. These are the facts which are to be presented, beginning with the most convincing, relating to the female sex hormone—œstrone.

Dating from the abundant supply of chemically pure œstrone, it has been possible to study in detail the biological action of this hormone which acts more particularly on the organs pertaining to, or allied more or less directly with, the genital apparatus—vagina, uterus, breast, prostate, hypophysis. This action is manifested by a cellular proliferation involving certain tissue hyperplasias (epithelial, connective and even muscular). The use of large doses, administered from an early age and continued for a long time, can cause these hyperplasias to end by becoming true tumours. Let us study several examples.

ŒSTRONE AND THE MAMMARY GLAND

The subordination of the histogenesis of the breasts to the secretion of the ovary is well known. The episodes in the breasts at the moments of puberty, menstruation, and pregnancy are conditioned by œstrone; the cyclic arrest of its production and the alternation of this secretion with other antagonistic hormones normally maintains the gland in a state of equilibrium. But if, by injections of œstrone, regularly renewed, one admits the organism of the mouse to the continued and predominant influence of this hormone, the proliferation of the mammary ducts which (exclusive of pregnancy) is only slight and temporary, continues further and is accelerated. The ducts dilate, ramify, and multiply; they form buds which become acini. After several months of treatment the mammary gland will have taken on a considerable development and this hyperplastic tissue will present all the signs of cystic dilatation and epithelial vegetation which characterize polycystic disease of the breast.

This proliferation is liable to go still further. It is known that the mouse is spontaneously subject to cancers of all forms, but the breast is the organ from which adenocarcinoma develops with particular frequency. For more than thirty years this cancer has served as the object of study for a large number of research workers. It is thus that it has been established

that one could, by appropriate matings, produce families of mice which are either susceptible or refractory to cancer. One thus succeeds in selecting a strain in which neoplasms are never observed; while, in another strain, adenocarcinoma of the breast appears spontaneously with great frequency. However, another interesting peculiarity, this tumour is almost exclusively feminine; in a family of which all the females die of breast cancer the males remain untouched. Histological examination of the breasts of these females which, a more or less long time after they have exceeded one-half of their life (beyond one year), develop an adenocarcinoma, shows that these glands present, more or less generalized, the state of cystic hyperplasia which a prolonged and predominant action of œstrone excites. There is nothing similar among the males, whatever their age, since their mammary glands have undergone from birth an arrest of development ending in their quasi-disappearance in the adult.

If, by the intervention of œstrone in the male mice, before their breasts are atrophied, one could prevent this regression, would not the production of cystic hyperplasia be observed, followed by adenocarcinoma of the breast, as in the female? This experiment has been done, and effectively gives this result. In strains which normally furnish a very high proportion of adenocarcinoma, the regular injection of œstrone, begun with the new-born, permits the following of an almost equal development in the breasts of the two sexes. Already after two or three months of treatment cystic hyperplasia is evident; the epithelium shows signs of proliferative activity, as seen by the presence of numerous mitoses; the newly-formed cells become irregular, and certain anomalies appear therein. After the fourth month cancers begin to appear in these animals, whatever the sex (often earlier in the males than in the females). Before they have reached one year, hence before the date when one would normally expect to see the appearance of adenocarcinoma in the females, all the animals will be dead of this affection. This result thus seems to furnish an experimental fact conclusive of a relation between the cancer and the hormone.

In reality the problem is not so simple as it would seem. Let us treat, under the same conditions, a litter of mice of a strain in which adenocarcinoma is never met with. The injections can be regularly continued throughout the total duration of life; certain animals will support this treatment and will attain old age without presenting mammary cancer. Histological examination will often show cystic hyperplasia, but without important or persistent activity of the epithelium. The mammary adenocarcinoma, which has as its immediate cause the prolonged action of an excess of œstrone, is thus subordinated to an hereditary factor which dominates the hormonal one. This observation cautions one not to draw prematurely from special experimental facts a therapeutic line of conduct, exaggerated or erroneous. It would be likewise falling into a similar error to consider a hormone (a substance naturally elaborated by the organism) as a dangerous agent, and to deprive patients of it for whom it is a useful medicament, on condition that it is properly administered.

ŒSTRONE AND THE UTERUS

Under normal physiological conditions the discontinuous action of œstrone on the vagina appears as the phenomenon characteristic of the œstrous cycle. But a continuous hormonal treatment will assure the maintenance of a stratified pavement epithelium, able to become hyperkeratotic because of the multiplicatory activity of the cells. In the uterus especially one easily observes the influence of œstrone on the principal anatomical elements—the epithelial lining, the glands, and muscle.

1. In the utero-vaginal passage, which in the mouse corresponds to the cervix uteri, the epidermoid transformation, observed in the vagina as a consequence of prolonged œstronization, likewise begins; after several months of treatment it can reach all the uterine canal; exceptionally, it has been encountered in the region of the epithelium of the tubes. Thickening, hyperkeratosis, hyperpapillomatosis of the epithelium of the cervix uteri have been observed by several authors in various mammals (notably in the female monkey) injected over a long time with œstrone. This state has been considered by many to represent a pre-

cancerous condition. Attempts have been made to activate the neoplastic process by associating with the hormonal treatment repeated local traumatisms. No verified case of epithelioma of the cervix has been obtained. In mice in which alternate injections of anterior hypophyseal extract and œstrone have been made proliferations of the metaplastic epithelium sending prolongations into the muscle have been noted in the region of the inferior cornu of the uterus. In one case the histological appearance of the tumour was that of an undoubted epidermoid epithelioma. Thus the attempts of various workers to reproduce experimentally a cancer very common in the woman, that of the cervix, by means of an hyperhormonal state, have been almost completely ineffectual. One might think that, here also, it would be necessary to associate this state with an hereditary predisposition. If one possessed a strain of mice susceptible to uterine cancer, as we possess a strain susceptible to breast cancer, perhaps one could augment the frequency and the precocity of the appearance of this tumour by keeping these animals in a hyperœstronic state.

2. In the first stage, one observes in the uterine cornua of animals subjected to high doses of œstrone a characteristic endometrial hyperplasia. If the treatment is continued for a long time the proliferation of the uterine glands becomes accentuated; they ramify, become cystic, penetrate the muscle, and even reach the subserous layer. If one adds to this a simultaneous reaction of the uterine muscle, first in the sense of a hypertrophy of its fibres, then in the appearance of an associated fibro-vascular reaction, one can see that these ramifications are susceptible of ending in the picture characteristic of fibro-adenoma of the uterus.

Finally, but rarely, attention has been drawn during the microscopic examination of such a uterus to glandular invaginations of exaggerated activity, presenting a scattered type of infiltration and a large number of mitoses, frequently of atypical aspect. One cannot avoid interpreting these pictures as the early signs of an adenocarcinoma of the uterine body.

Summarizing, if experimentation has permitted the reproduction of the picture of several gynæcological affections, the cause of

which seems to reside in a vitiation of the secretions of the ovary, it has not succeeded in obtaining the cancerization of the uterus in a series of observations.

ŒSTRONE AND THE PROSTATE

Bound by habit to define œstrone as a female sex hormone, we have difficulty in realizing that it is also found in the normal male organism, and that it would even be susceptible of exercising an action therein. Experimentally, it is certain that, injected into the male, it induces changes in the morphology of certain organs of the sexual apparatus, in the same sense that it does so in the more or less corresponding feminine organs. It is thus that under the influence of a prolonged œstronization is produced a fibro-muscular hyperplasia of the vas deferens and of the tunics of the adnexal glands, such as the seminal vesicles and prostate. Moreover, the epithelium of certain glandular ducts in the posterior portion of the prostate presents a metaplasia identical with that which the same treatment produces in the uterus; the cylindrical epithelium becomes a stratified pavement epithelium; little by little this extends and cornification increases. All of this ends in establishing a hypertrophy of the prostate, causing, in the mouse, a urinary retention with all of its classic sequelæ. These results have suggested to certain authors a hormonal pathogenesis of prostatic hypertrophy in man. Due to the regression of the male hormonal secretions with age, it could happen, at a certain period, that a preponderance of œstrone exists, producing a fibro-muscular hyperplasia of the prostate. Certain epithelial cancers of this gland, of epidermoid structure, difficult to interpret up to the present, could be explained in this manner. Let us note in any case that the production of a genuine cancer of the prostate in the animal has not as yet been possible.

ŒSTRONE AND THE HYPOPHYSIS

The problem of the secretory inter-relations of the hypophysis and the gonads still remains obscure. However, it is not doubted that the ovarian gland is controlled by the hypophysis. Conversely, the modifications which pregnancy, castration, and injections of œstrone induce in the structure of the anterior hypophysis, show

that the pituitary is not absolute sovereign, but that an endocrine equilibrium is assured by a balance of play of the secretions of the two glands in question. In regard to the cystological changes produced in the hypophysis by injections of œstrone the results are contradictory, at least in the case of a treatment of short duration. But there is agreement in admitting that a very active œstrogenic substance, administered in large doses over a long time, considerably modifies the structure of the gland. These changes are evident (1) in the capillaries, which dilate, the walls of which thicken and become rigid, so much so that they remain widely open, even though empty of blood; to an extreme degree they are transformed into true small lacunæ; (2) in the production of colloid which increases considerably in the intermediate as in the anterior lobe, accumulating in the hypophyseal sulcus; (3) in the cells of the anterior hypophysis there is a multiplication of the chromophobe cells, which gradually replace the granular cells, the basophilic cells disappearing first, followed by the acidophilic cells. The vascular congestion and the cellular multiplication combine to augment the volume of the anterior lobe, which becomes globular, reflecting upward the two other lobes. Finally, in mice treated for more than a year this hypertrophic process can end in the formation of true chromophobe adenomas of the hypophysis.

Since the coincidence of such hypophyseal adenomas and mammary adenocarcinomas has been noted, is it possible to admit a direct relationship between these two tumours? Is there a basis, for example, to envisage the development of a neoplasm of the breast due to secretory disturbances in the pituitary? It does not seem so, at least in the present state of our knowledge. In effect, this coincidence is far from being the rule. In mice which early develop a mammary adenocarcinoma the hypophysis may have preserved an apparently normal structure. On the other hand, considerable changes in this gland, even to the point of formation of adenomas, are encountered in older mice whose breasts present no sign of neoplastic activity.

THE ROLE OF THE HYPOPHYSIS IN THE GROWTH OF TUMOURS

If the facts seem to reply in the negative to the preceding question of the relation between

hypophysis and mammary cancer, they ought, nevertheless, to have been brought forward, for there are other experiments which speak in favour of a general rôle of the hypophysis in the growth of tumours. In the last twenty years much work has been devoted to this study. In these, varied experimental measures have been utilized to react on the pituitary secretion, either by injections of hypophyseal extracts, or, more recently, of allied physiological substances from the urine; or, again, by inhibiting through hypophysectomy or irradiation the pituitary secretion. But the efforts of research workers have not succeeded in establishing a solution, the results obtained being squarely antagonistic. These contradictions may in large measure be explained because of the use of cancerous grafts as experimental material. The cells of a transplanted tumour, if they are capable of adapting themselves to a different organism, can be cultivated there, but they will always remain genetically foreign. Thus the graft will retrogress under influences which are incapable of modifying the cells of a spontaneous or induced cancer, which belongs truly to the individual affected. It is well to recall once again the care with which it is necessary to observe when one transposes the results obtained with transplants into the domain of cancers which have appeared *in situ*.

What does experimentation show in tumours originating *in situ*? One can very simply destroy the pituitary of the rabbit with radon, in which animal one can produce certain tumours. This can be accomplished by the regular cutaneous application of tar. Thus, in rabbits without the hypophysis the applications produce only the late appearance of rare cornified vegetations, which remain limited and have a tendency to spontaneous elimination. This reaction is slight in comparison with that which takes place in control rabbits, on which numerous papillomas develop in 3 or 4 months, a certain number of which become epitheliomas. The same inequality of effect is produced if one uses in the place of tar a synthetic hydrocarbon such as benzopyrene. Here too proliferations of the epidermis, scarcely noticeable in the animals operated on, remain considerably retarded as compared with those of the controls.

Finally, one can utilize the experimental tumour recently acquired, precious for research, whose origin is due to the workers of the Rocke-

feller Institute. The infectious papilloma of the rabbit is not a cancer but, like other benign tumours, it is capable of becoming malignant under certain influences. The causal filterable agent, inoculated into the cells of the epidermis of the rabbit, provokes the appearance of a rapidly growing cutaneous mass, ending after several days in the production of exuberant cauliflower formations. The inoculation of rabbits whose hypophyses have been destroyed permits the appearance of papillomas in the normal time, but, as a rule, these either retrogress spontaneously or they remain relatively small.

A process hastening the cancerization of the cutaneous papillomas of the rabbit consists in first causing their appearance with tar, then injecting intravenously into the animals thus treated the virus of the infectious papilloma; in several weeks the malignant transformation is accomplished. If we repeat the same experiment in rabbits whose hypophyses have been destroyed, the small epidermal excrescences produced by the tar undergo no modifications as a result of the injection.

Without doubt, it would be imprudent to draw any general conclusions from these few experiments, but their results seemingly accord favourably with the hypothesis of the intervention of a hypophyseal hormone which permits tumoural growth.

DISCUSSION AND CONCLUSIONS

Concerning the ensemble of the question of the relations between hormones and cancer it seems established experimentally that such a relationship exists, but the facts are still too few to permit of a lengthy discussion. The conclusion of this exposé must, therefore, only be reserved. But such a problem, that of the mechanism of cancerization, arouses so strongly the curiosity of every one that apropos of any new subject one asks himself what knowledge, however small it may be, can be drawn upon to give enlightenment.

The histological study of organs, taken from animals submitted to more or less prolonged treatments with a hormone such as œstrone, permits the reconstruction of all the steps which, in certain cases, can terminate in cancer. But cancer, from whatever element it takes its origin in an organ, will not appear suddenly

and without preparation. The sensitive cell reacts to the hormone by repeated multiplications. If this action is prolonged beyond the normal physiological limits a tumoural process will result from this persistent proliferation, at least if the organism does not itself oppose to this exciting substance an antagonistic substance (secretory product of another gland, or perhaps a special product elaborated through reaction?). But whether it is called hyperplasia or tumour, the organic lesion provoked is at first of a benign nature.

When and how is the malignant transforma-

tion produced? Therein remains the entire question, as it is seen every day in the clinic and experimental cancer research. Once again one is permitted to say that, as here, cancerization appearing in a tissue during the course of accelerated and long repeated multiplications, presents itself as a disease of cellular division. Moreover, in the case considered, it is certain that the beginning of the affection is favoured by a special predisposition, allied to heredity. The intervention of this factor, the nature of which remains entirely unknown, does not simplify the problem.

A MACROCYTIC ANÆMIA ASSOCIATED WITH RHEUMATIC INFECTION*

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THAT the anæmia seen in association with acute rheumatic fever may be of severe degree is indicated in Osler's¹ statement concerning the blood changes in this disease—"The blood is profoundly altered, there is no acute febrile disease in which anæmia occurs with greater rapidity", and in Poynton's² remark that in rheumatism, "Severe, even fatal, anæmia may result". Watching the occasional case of acute rheumatic fever, one is often struck by the rapidity with which the pallor due to blood changes may develop, yet signs of active hæmolysis are often lacking, and the patient presents more the picture of an anæmia without deposition of pigment in the eyes or skin.

Whether in the anæmia associated with a true chronic rheumatic infection we may have to deal more often with a depression of the bone-marrow function than with a persistent hæmolysis cannot be said, though in the course of the chronic arthritides a simple chloranæmia of microcytic type is the usual finding. In the case we are reporting, the striking pallor, the absence of pigment deposits, the negative van den Bergh tests, and the low readings of urobilin suggested interference with the proper manufacture of blood, rather than the breaking-down of the newly-formed cells, while the macrocytic

picture of the blood smear and the high colour-index continually suggested the existence of a true pernicious anæmia.

There are but few reports which deal with the state of the bone marrow in a chronic rheumatic infection. Yet, recognizing how widespread may be the rheumatic invasion in the body, an active involvement of the blood vessels in the marrow may, at times, be assumed to occur, and, recognizing how varied may be the response of the bone marrow to different types of stimulant, one might be prepared to meet with more or less unusual responses as concerns the blood picture should this rheumatic invasion be affecting the vessels in the blood-forming organs for any length of time.

The type of anæmia most often described as occurring in the course of an acute rheumatic attack conforms most readily to the hypochromic, a type in which the poorly-filled cells are, in gross, smaller than normal—a hypochromic microcytic anæmia. Few, if any, records are available, however, which tell us what might be expected during the course of a long continued rheumatic infection, but the impression one receives in reading descriptions of the blood condition in this disease leads one to suggest that the blood picture in both the acute and chronic type of case will be much the same. Records of the state of the gastric secretion in rheumatism, either acute or chronic, are not available.

* From the Department of Pensions and National Health, Christie Street Hospital, Toronto. Presented at the Section of Medicine, the Academy of Medicine, Toronto, December, 1935.

With the idea in one's mind that the blood response in the rheumatic infection would be one showing some distinctly hypochromic microcytic picture, it was interesting to find that in a case which came before us the underlying cause of an anæmia of macrocytic type was probably a long continued and very diffuse rheumatic invasion, which in some way produced a picture in the circulating blood closely resembling that of a pernicious anæmia. The rheumatic background of the case in question can be briefly stated.

CASE REPORT

C., a soldier in the Great War, a man of good mentality and splendid physique, had been discharged from the army in 1919 with a diagnosis of "disorderly action of the heart" of unknown origin. He presented none of the general features which are usually associated with men who are subject to this well-known disorder. He was a hard, keen worker, but complained persistently of palpitation, dyspnoea on exertion, weakness and occasional attacks of pain about the heart. He remembered no rheumatic manifestations in his childhood but had had a mild attack of arthritis during the war. After his discharge, and over a period of 10 years, he had had several mild attacks of arthritis, affecting the fingers, knees, ankles and toes, and as an interesting feature of his long continued ill-health, mentioned that he had "hundreds of nodules under the skin and on the tendons of various muscles". The recollection of the appearance of these nodules did not come to him however until the final weeks of his illness, nor were the nodules themselves ever shown to the many examiners before whom the man came for investigation and treatment. In 1929 an outside physician made the note that there had been an outbreak of "multiple thromboses" in many parts of the body, but with the exception of this detail and the persistently rapid heart

action there was singularly little upon which to make an absolute diagnosis, and the note made by the outside physician came to one's attention too late in the course of the man's illness to give us any useful suggestions.

In his many appearances at the out-patient clinic over a period of nearly thirteen years, C. had made no complaints save that of the easily induced dyspnoea and rapid heart action. Arthritis was never stressed. He presented the appearance of a well nourished man, and though, as a last resource, hyperthyroidism was considered as a cause of his rapid heart action, yet a normal basal metabolism and a preservation of weight during his long illness spoke strongly against a diagnosis of thyroid disease. An occasional wave of low-grade fever was noted, but nothing was found in the course of a long investigation which might explain a rather distinct pallor, the rapid heart action, and the dyspnoea. Blood cultures were repeatedly negative, as was the Wassermann reaction. Careful tests of kidney function gave no clue, and even the pallor itself was not associated up to the last months of his illness, with any material reduction in hæmoglobin or red cells, or with any elevation of the white cell count which might suggest infection. The pallor, and the retention of nutrition and fat layers suggested, perhaps, a hypothyroid state, but the rapid heart action and the normal basal metabolic tests seemed to dispose completely of any such idea.

Early in April, 1933, the blood count indicated that a distinct anæmia was developing. The patient complained of being unusually weak, and the blood count at this time was reported as, hæmoglobin, 53 per cent; red cells, 2,400,000 per c.mm.; white cells, 7,500; platelets scanty; and a note from the laboratory accompanying the report says, "blood in its count and in the examination of the stained smear suggests very strongly the existence of a pernicious anæmia". The differential count of the white cells showed no departure from normal. A comparison of the man's clinical condition with his laboratory findings did not endorse the laboratory's suggestion, as the man appeared white rather than pigmented, and had none of the physical signs usually associated with pernicious anæmia. Further tests in the laboratory, moreover, showed that he possessed a normal amount of free hydrochloric acid in his stomach contents,

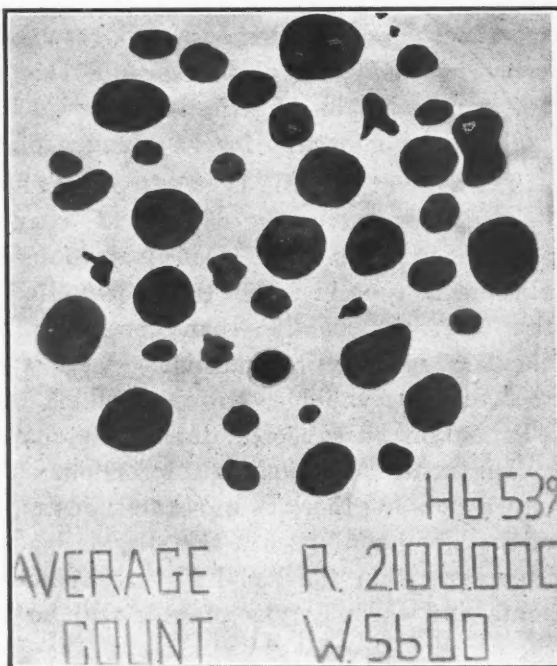


Fig. 1.—A macrocytic anæmia with chronic rheumatic infection.

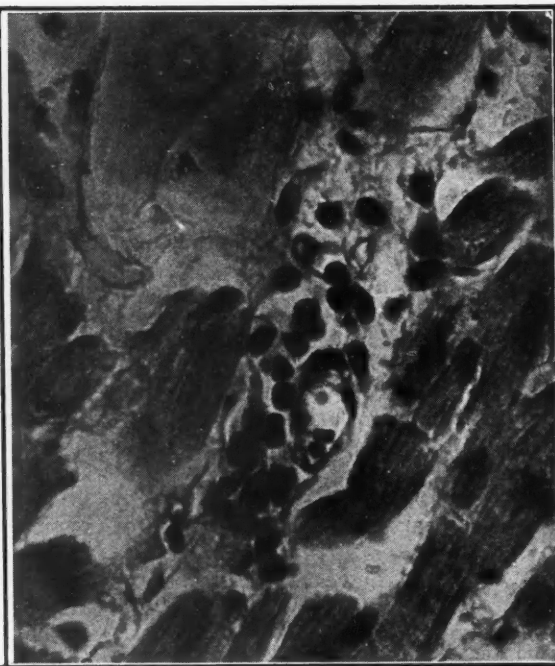


Fig. 2.—Aschoff body in heart muscle (high power).

that the van den Bergh reaction was not in the least suggestive, and that there was no excess of urobilin in the urine. Intensive therapy with powdered liver extract produced a suggestive rise in the reticulocytes from 2 to 10 per cent, the higher percentage being retained for several weeks while he was under treatment. A further result of this treatment, to which large doses of iron and ammonium citrate were now added, was the raising of the hæmoglobin to 60 per cent, though little or no change took place in the number of the red cells. On more than one occasion the laboratory made the suggestion that "the blood smear suggested strongly pernicious anæmia".

As late as April 23, 1933, no murmur suggestive of rheumatic valvular disease had been heard, and this in spite of the fact that the man had appeared before the heart clinic of our own and other hospitals. On this date I made the note that a presystolic mitral murmur had revealed itself, yet a few days later the murmur did not seem to be in evidence. The patient was not seen now for two months, and when returning brought the history of having had a very active inflammation of the muscles of the forearms. At this time the presystolic murmur at the mitral area was easily found by all examiners, and as the patient showed several distinct subcutaneous fibroid nodules, some distinct soreness of the small joints of his hands, and a slight fever, the diagnosis of a true rheumatic condition seemed certain. Early in October, 1933, he appeared for admission, evidently seriously ill with fever, multiple fibroid nodules on the tendons and about the joints, and a few suggestively reddened and tender nodes more like erythema nodosum. He complained that there had been a steady heart pain for a matter of ten weeks and that of late dyspnoea had been extreme. Further examination showed that in addition to the murmur of stenosis at the mitral valve the heart was very evidently enlarged, that a systolic murmur had developed, and that there was a faint but distinct to and fro pericardial rub at the lower sternum. The pulse rate was rapid, 140, the blood pressure was extremely low, 90/60, and there were signs of beginning consolidation at the base of the right lung. The only change in the blood picture, as compared with previous examinations, was that the white blood count had risen to 50,000 per c.mm. The hæmoglobin was 45 per cent; the red cells, 2,730,000, (in spite of persistent liver therapy) figures now more suggestive of a secondary anæmia, yet the blood smear still preserved its macrocytic character.

With the history detailed, particularly with the profuse eruption of fibroid nodules, one inclined more to the idea that we were witnessing an acute flare-up of the rheumatic infection rather than the development of a rapidly progressive sub-acute bacterial endocarditis. In this connection one noted the absence of any gross enlargement of the spleen and of the common embolic manifestations seen in the subacute bacterial endocarditis, as well as the persistently negative results from blood cultures. The presence of albumin, casts and red blood cells was looked upon as something occurring in association with an outspoken pneumonia which had now developed at the right base.

During the week of the final stages of his illness fibroid nodules appeared in great numbers. Outspoken signs of pneumonia with high, steady temperature were in evidence. There was no suggestion of progressing kidney damage, the non-protein nitrogen never rising above 40. An extensive pericarditis complicated matters and the heart failed rapidly. The patient died in active delirium. Repeated blood cultures remained sterile. The skin manifestations were never those of sub-acute bacterial endocarditis, being more particularly profuse eruptions of erythema nodosum. There were at no time any Janeway's spots or Osler's nodes.

Post-mortem examination disclosed an outspoken pneumonia of the right lower lobe, a diffuse shaggy pericardial exudate, a much enlarged heart, particularly

as to the left side, well established stenosis of the mitral valve with marked thickening, and indications that this stenosis was of long duration. About the edge of the stenosed and thickened valve were to be noted small warty growths, suggestively rheumatic, and on the wall of the left auricle could be seen a small patch of warty endocarditis. There was nothing in the valves or endocardium to suggest that a sub-acute bacterial process had been imposed upon the rheumatic condition. Smears and cultures from the valvular growths were negative. The other valves of the heart were unaffected. The distinctly thickened heart muscle was softened and brown. The lining of the aorta showed some willow markings. The coronary arteries were patent. Both liver and spleen were enlarged. The changes in the kidneys were more those of an acute nephrosis than of a progressive nephritis. As has been noted in connection with post-mortem examinations, in cases dying as a result of acute rheumatism, it seemed impossible to find the fibroid nodules after death, a detail often noted and one which is quite in keeping with their rapid appearance and disappearance.

Careful microscopical examinations were made of tissues removed looking naturally for evidence of the rheumatic infection. Throughout the heart muscle characteristic Aschoff bodies were found in abundance. Careful search failed to determine their presence in the blood vessels or alveoli of the lungs. The thickened pericardial layer showed an infiltration consisting more particularly of mononuclear cells, with here and there collections suggestively like Aschoff bodies (Fig. 2). There was no suggestion in the sections of liver, spleen or kidneys of a rheumatic process.* The middle coat of the aorta showed a patchy infiltration of mononuclear cells, perivascular in situation. The bone marrow was red and hyperplastic in appearance, and seemed to show under the microscope an active cellular reaction in its capillaries and stroma. Numerous nucleated red cells were to be seen, more of the normoblastic type. Megaloblasts were not in evidence.

Nothing save the rheumatic infection seemed to lie behind the year-long history of rapid heart action and the acute anæmia of more recent origin, though whether we had to deal with a rheumatic deposit in the vessels of the bone marrow or whether the chronic poisoning from the prolonged rheumatic infection elsewhere in the body produced the curious blood picture we are unable to say. Some departure from the normal is in evidence in the bone-marrow section, and the marrow of even the long bones was red and hyperplastic as might be expected in the case of an anæmia due to some chronic infection. Why the cells extruded from the marrow should be in great part macrocytes cannot be readily answered. It is to be remembered when mentioning the absence of megaloblasts in the bone-marrow section that the patient had been under liver treatment up to two weeks before his death, though from his history and general appearance there had never

* Referring to the question of macrocytic anæmia associated with certain diseases of the liver, we noted in the gross and microscopical examination no evidence of cirrhosis.

been any suspicion in our minds that he suffered from pernicious anæmia. The failure to respond to treatment, the absence of any signs of cord changes, the presence of free hydrochloric acid in the stomach, the low icteric index, and the failure to show urobilin in the urine would seem to justify this attitude.

The anæmia being, as we concluded, a manifestation of a true persistent rheumatic infection or intoxication, it was interesting to find that it did not fit well into the picture of the anæmias usually associated with such conditions. Following Haden's³ classification, one would describe it as a macrocytic normochromic, or a macrocytic hyperchromic anæmia, terms which are self-descriptive. The colour-index was always 1 or 1 plus; the cells were well filled and highly coloured. The variation in size of the individual cells was extreme and the macrocytosis allowed the diameter of the red cells to reach here and there 8 to 10 microns. As one looked at the film with its scarcity of white cells, its scanty platelets, and irregular, deeply coloured red cells, the suggestion of pernicious anæmia came at once forward, a suggestion which, however, was not borne out by the course of the patient's illness, or by his response to treatment, or by the general findings.

Macrocytic anæmias are by no means rare and in the past have been frequently confused with the true Addisonian anæmia. Reports of cases of macrocytic anæmias in conditions other than pernicious anæmia have been appearing with considerable regularity in recent years, and one finds in addition to the cases of macrocytic anæmia we are used to associate with pregnancy, with intestinal parasites, with sprue, with acholuric jaundice, and with some ill-defined hæmolytic conditions, that many cases are being reported of macrocytic anæmias caused apparently by conditions which more usually give rise to blood changes of the microcytic and hypochromic type. Such for instance are the cases reported by Baldrige⁴ and by Haldimann⁵ of macrocytic anæmia following the persistent use of aniline in hair dyes, the many cases seen in association with metastases and tumours of the bone marrow,⁶ and the cases of macrocytic anæmias occurring in the course of various liver diseases.^{7, 8} We have in recent years had our attention drawn to a macrocytic anæmia, strongly suggestive of the pernicious

anæmia picture, associated with resection of the stomach and with gastro-intestinal anastomoses, and to the macrocytic anæmia reported as occurring with great frequency amongst the women of British India.⁹ These latter forms of anæmia, intimately connected with defective absorption and utilization of the specific anti-anæmic factor or with food and vitamin deficiency are frequently found associated with achlorhydria, which adds materially to their resemblance to true pernicious anæmia.

Such macrocytic anæmias may be at times particularly difficult to classify. The classification may be made somewhat easier, however, by removing from the large group of these macrocytic anæmias, those cases whose blood conditions are shown by bone marrow examination to be megaloblastic as well as macrocytic.* Such blood and bone marrow findings are moreover usually found to be associated with deficiency of the specific anti-anæmic factor in the stomach, with its defective absorption, or with its ineffective storage or utilization. One notes, however, that some of the diseased conditions which are producing the megaloblastic macrocytic picture are now recognized as being curable by specific treatment. Others, such as those due to malignant disease of the intestine, extensive resections of the stomach, cirrhosis of the liver are likely to show only a temporary improvement, and differ from the other members of the group in this particular. Removing this large group of macrocytic anæmias with their megaloblastic bone marrow findings from the general field of macrocytosis, one is left with an ill-defined group of macrocytic anæmias which, to begin with, do not respond to specific liver treatment, and which do not seem to be associated with dietary deficiencies or with deficiency in the specific anti-anæmic factor or with its defective absorption or utilization. In this group are found cases of hæmolytic anæmia, of anæmias with acholuric jaundice, of anæmias due to malaria and to lead poisoning, cases of anæmias in which the bone marrow is irritated by metastatic deposits, infections and toxæmias of various

* According to Isaacs,¹⁰ megaloblasts are to be found in the bone marrow in all forms of anæmia. A special technique is described. From his findings Isaacs concludes that the megaloblast is a normal stage in the production of the erythrocyte rather than a pathological or fetal cell.

character, such, for instance, as in the case we are reporting. The macrocytic anæmia associated with the conditions just mentioned is usually linked up with a bone marrow which has remained normoblastic, as opposed to the megaloblastic bone marrow seen in pernicious anæmia; it may, in many cases, disappear if its cause is found and removed and if proper treatment is instituted. As a general rule it does not respond to specific anti-anæmic treatment with liver and stomach preparations.

It is probable that prolonged rheumatic infection had most to do with producing the curious blood picture presented by our case. The careful autopsy revealed no suggestion of other associated conditions. True pernicious anæmia certainly did not exist, and one is brought to the conclusion that the rheumatic process or the poison of rheumatism may occasionally act as do other toxic agents in producing a type of anæmia rather departing from the standard set in the usual run of secondary anæmias.

In discussing the anæmias met with in carcinomatosis affecting the bone marrow, Waugh⁶ suggests that there may be extensive embolization of the vascular channels of the myeloid tissue by tumour plugs with consequent profound circulatory disturbances and hæmorrhagic extravasations. A generalized alteration in the blood-forming activity results from this embolization which may lead to the changes necessary for the production of anæmias. In

the group of cases he describes, however, typical hæmolytic anæmias seem to have followed the tumour deposits in the bone marrow. Judging from the many reports in the literature, almost any form of anæmia may be associated with involvement of the bone marrow in malignant disease, and the picture of true pernicious anæmia is often reproduced in the blood specimen. Knowing that one of the manifestations of true rheumatism may be the occurrence of multiple thromboses in the smaller vessels, it is possible that we may yet be able to demonstrate a rheumatic invasion of the bone marrow with multiple areas of irritation. We were unable, however, in our case to find lesions in the blood vessels of the bone marrow which might be called truly rheumatic.

REFERENCES

1. OSLER, W.: Principles and Practice of Medicine, Appleton and Co., New York.
2. POYNTON, F. J.: Osler's Modern Medicine, Vol. 2, Lea and Febiger, Phila.
3. HADEN, R. L.: Methods and clinical value of determination of size of red blood cell, *Am. J. M. Sc.*, 1931, 181: 597; *ibid.*, Classification and differential diagnosis of anæmias, *J. Am. M. Ass.*, 1935, 104: 706.
4. BALDRIDGE, C. W.: Macrocytic anæmia with aplastic features following application of synthetic organic hair dye, *Am. J. M. Sc.*, 1935, 189: 759.
5. HALDIMANN, J.: Contribution à l'étude des intoxications par l'aniline. Anémie aplastique grave dans un cas d'intoxication chronique, *Schweiz. med. Wchnschr.*, 1929, 59: 838.
6. WAUGH, T. R.: Hæmolytic anæmia in carcinomatosis of the bone marrow, *Am. J. M. Sc.*, 1936, 191: 160.
7. ROSENBERG, D. H.: Macrocytic anæmia in liver disease, etc., *Am. J. M. Sc.*, 1936, 192: 86.
8. WRIGHT, D.: Macrocytic anæmia and hepatic cirrhosis, *Am. J. M. Sc.*, 1935, 189: 115.
9. DAVIDSON, L. S. P.: Pernicious anæmia and other macrocytic anæmias, *Brit. M. J.*, 1936, 1: 804.
10. ISAACS, R.: The bone marrow in anæmia: The red blood cells, *Am. J. M. Sc.*, 1937, 193: 181.

PSYCHOSIS FOLLOWING POST-TRAUMATIC EPILEPSY

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COMPLETE recovery from epilepsy of severe degree is all too rare an occurrence. Relatives invariably suggest the possibility of head injury as being the causal factor, and hope, too often in vain, that a "brain operation" will result in a cure. The following case record is of interest insofar as the causal factor did prove to be of traumatic origin, although in the beginning there was no reason to suspect it. The patient is of further interest since he was ad-

mitted to hospital suffering from a psychosis and had been recommended for commitment to a mental hospital. The clinical picture was apparently not different from that commonly diagnosed as schizophrenia. At that time no history of the preceding convulsions was available, and in the absence of neurological signs there was no suggestion of a localized brain lesion. Hence, the discovery of the underlying factor in the form of brain scars, the excision of these, and

the sustained good health since then form a series of events that seem worthy of record.

CASE REPORT

The patient, a man of 21 years, was admitted to hospital on February 11, 1930, with an acute psychosis, presumably of short duration but without further history. On admission he was noisy and abusive, swearing, and offering to fight those around. With reference to this conduct he stated he was acting like his father; later it was learned the latter was long dead. Some fleeting visual hallucinations were present whose content could not be elicited. After four days he became quieter but continued to talk in an irrational fashion and showed emotional fluctuations of hilarity and depression. He was suspicious of the nurses and believed he was the object of various forms of persecution. Auditory hallucinations were also present and he talked in response to "the voices", one of which was that of his mother; later it was discovered she was dead also. At the end of a week he claimed he had "come to himself" and that his mind was now clear. However, he continued to behave and talk in a psychotic fashion, claiming acquaintance with visiting students and calling them by fictitious names. There was amnesia for the preceding two months. When engaged in conversation he spoke much of his childhood, showing much emotion in references to his mother. He also continued to have incontinence of urine.

Physical examination was negative in all respects, and the case appeared to be an acute schizophrenic psychosis. However, he had made passing references to "weak spells" which aroused our curiosity and it was decided as a matter of experiment to note the possible results of hyperventilation. The results came as a surprise and were as unexpected as could have been imagined.

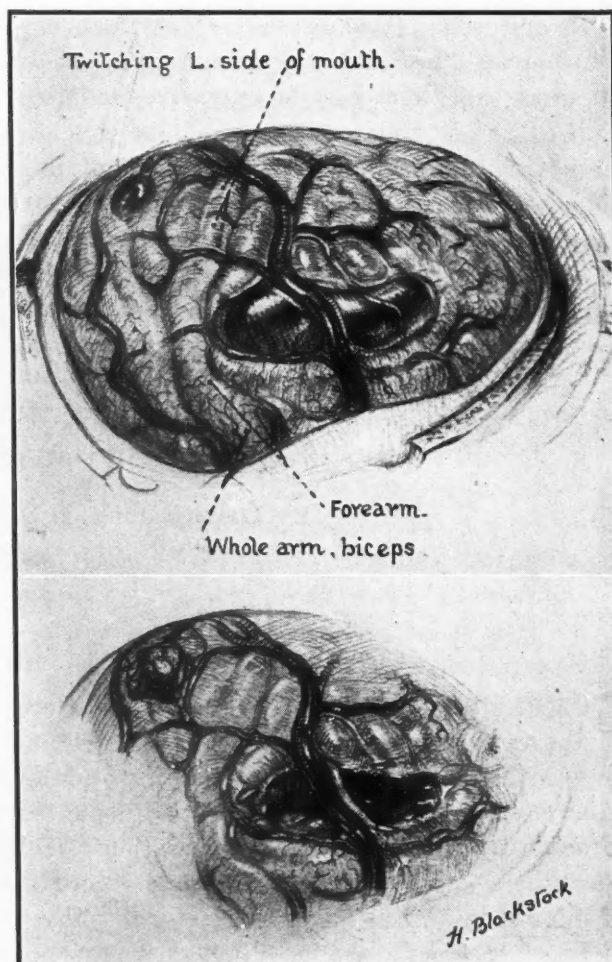
Hyperventilation test.—After hyperventilating for about five minutes, in which he cooperated fairly well with encouragement, the following changes occurred. He began to complain of a feeling of stiffness in the left arm and leg, and examination revealed rigidity in those limbs. Then the following phenomena were noted—increased bicipital and patellar reflexes on both sides, bilateral ankle clonus, absence of the left abdominal reflex and absence of the plantar reflex on the left side, although a flexor response was present on the right. An acute emotional outburst then occurred, with marked flushing of the face and he called out for his brother. This was followed by turning of the body to the left. Weakness of the left side of the face was then noted. It should be noted that the facial paresis affected the brow as well as the lower part of the face, as was evident when he was asked to frown and elevate the eyebrows. He was referred to the neurosurgical department for further study of the nature of the cerebral lesion that obviously was present.

Encephalography.—Air was injected by the lumbar route to a total of 120 c.c., the initial spinal fluid pressure being 140 mm. of water, and 110 c.c. of fluid were withdrawn. During this procedure the patient showed much sweating and flushing, and the pulse pressure was increased. Examination of the x-ray films showed two cystic collections of air on the right side of the brain, one in the parietal, the other in the frontal region. A diagnosis was made of cyst formation in association with brain scars.

Condition before operation.—By the time of operation the patient was quiet in conduct. However, he was still out of touch with his surroundings and his memory was very defective. In addition to inability to recall events of the preceding two months he could not remember events from day to day. Thus, for example, he had no recollection of a spinal puncture on the day following. He could only recall a few

events since admission, such as having used "rough words", and of having shouted for his brother. This referred to his statements at the end of the hyperventilation test. In general he still showed a tendency to waywardness and occasional truculence. The paresis of the left side of the face and a transient bilateral ankle clonus had persisted since the hyperventilation test and were present on the day of operation, that is, ten days after the test.

Operative procedure.—A right, mid-parietal, osteoplastic flap was planned to uncover the two cystic areas with a transverse measurement of 11 cms. The flap was turned down without difficulty. Over the parietal scar the dura was very vascular and bled freely on elevation of the flap. A dural flap with pedicle toward the midline was outlined and freed from the underlying scars by careful blunt dissection. The brain scars were excised by the thread excision method and by suction and sharp dissection. In the parietal region the large vein described below was freed from the underlying scar and thus left bridging the cavity; one bleeding point on it was controlled by a muscle graft. A small artery accompanied the vein, and a bleeding point on it was also controlled by muscle graft. When excision of the two scarred areas was completed the cavity in the parietal region measured about 3.5 x 3 cm. and that in the frontal region about 2 x 1.5 cm. Before excision the motor areas had been outlined by galvanic stimulation. Faradic stimulation was also applied to the scarred areas and to the vessels of these areas. No convulsion resulted, but stimulation of the vessels in each scar with the faradic current was followed by definite



Right cerebral hemisphere.
Removal of cicatrices.

flushing of the cortex. The dura was sutured tightly and a rubber tissue drain placed beneath the bone flap over the dura and carried out through a stab wound. The bone flap was wired in two places and the scalp was closed in two layers in the usual way.

Pathology.—Intracranial tension was not increased. The dura was adherent to the arachnoid over the two scarred areas, and many fine vessels, both arteries and veins, ran from the brain to the dura, so that the latter was separated with difficulty. When the dura was peeled off no collapse of the underlying brain occurred. The two scarred areas were cystic and yellowish in appearance before the arachnoid was opened; they were apparently covered by arachnoid, pia and a thin layer of brain. When opened the cyst-linings were found to be smooth and glistening, and the underlying nervous tissue was very firm. The cyst in the right lower frontal region measured about 1 cm. in depth and diameter, that in the parietal region was irregular in outline and measured, with the scarred brain tissue, about 3.5 cm. in length and 2.5 cm. in depth. The parietal scar was crossed by a large vein just behind the post-central convolution.

Condition after operation.—After the operation a convulsion occurred the same day and another four days later. These were the only convulsions that occurred during his stay in hospital. A second hyperventilation test was done a month after the operation. Before this test the only abnormality present was a deviation of the jaw to the right on opening the mouth. After hyperventilating for eleven minutes bilateral ankle clonus, increased right knee jerk, slight rigidity of the left arm and paresis of the left side of the face appeared. The facial paresis affected the brow as well as the lower part of the face, as was also noted after the first hyperventilation test. The ankle clonus persisted for an hour, as did the facial paresis. The patient was discharged from hospital six weeks after the operation, and the only abnormalities then present were a deviation of the jaw to the right on opening the mouth and absence of the left upper abdominal reflex.

Additional history.—Shortly before operation a history was obtained of the events preceding admission to hospital. On the third day before admission the patient had three convulsions with loss of consciousness and between the convulsions he was stuporous. Later, in bed, he had five further convulsions. On the following day he was mentally dull and exhausted and had two convulsions in the forenoon. In the afternoon he became mentally confused and kept calling for his brother. On the day of admission to hospital two convulsions had occurred. Mental confusion, visual hallucinations and alternate laughing and crying followed, this being his condition when admitted.

Inquiry as to the preceding years revealed that in November, 1927, he knocked his head while passing through a cellar entrance and was stunned for a few minutes. Four weeks later twitching of the left side of the mouth began to occur, and later these attacks of twitching affected both sides of the face. An x-ray of the skull was made and showed nothing abnormal. One year after the accident he had a convulsion with loss of consciousness. Convulsions continued to occur and by about six months previous to admission were accompanied by biting of the tongue and urinary incontinence. Also at this time it was noted that for four or five days preceding a convulsion a change in personality occurred, and he tended to be irritable and domineering. However, no psychotic phenomena had ever appeared.

Progress.—Since leaving hospital the man has remained free from convulsions and from mental abnormality of any kind and has continued at work in a normal fashion. Some time ago he reported a happy and successful marriage with the issue of a son. He

has built himself a home, and plans to enlarge this, all of which would substantiate that the restoration to normality is both enduring and complete.

COMMENT

The history is interesting in showing the development of serious results from an apparently minor head injury. In spite of the apparently trifling nature hæmorrhages had occurred, with subsequent scarring and cyst formation in the parietal and frontal regions.

The psychosis was similar in form to cases commonly diagnosed as schizophrenia. It is interesting to note that the patient's mental experiences and expressions related largely to his early home life and to his family. Thus, in his aggressive moods he spoke of himself as behaving like his dead father; the auditory hallucinations had reference chiefly to his dead mother; and in emotional outbursts, both before admission and after the first hyperventilation test, he called for his twin brother from whom he had been separated for many years. The amnesia is also worthy of note. Thus, while he claimed to "come to himself" at the end of the first week, he continued to have amnesia for the preceding two months and also was failing to recall the day-to-day occurrences. On discharge from hospital he had only vague and isolated memories for a large part of his stay here.

One other point to be noted is the occurrence of a total left facial paresis after the first hyperventilation test. This is contrary to the usual teaching as to the effects of cortical lesions on the activities of the facial nerve.

SUMMARY

1. In a patient with a psychosis diagnosed as schizophrenia neurological changes indicative of a localized brain lesion were manifest after a short period of hyperventilation.
2. After verification by encephalography and x-ray, exposure of the brain revealed cystic areas in the right parietal and frontal regions. These were excised by thread excision, suction, and deep dissection.
3. The history obtained revealed that the psychosis had developed after a series of epileptic convulsions. These convulsions had been occurring for three years and developed after a head injury of apparently minor nature.
4. The patient has been free from convulsions or mental abnormality since the operation, and has lived in a normal, well adjusted fashion.

SCLERODERMA WITH CALCINOSIS*

By

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TO a student of medicine a new clinical experience always gives a thrill. Even the most blasé hospital physician is learning something new each day though he may not be prepared to admit it; certainly at least once a month he is faced by some problem that has not confronted him before. Such was my position early in January, 1935, when on making my daily ward visit I was shown the patient whose case report I am about to relate, and realized that the condition was a new one to me.

CASE 1

Mrs. K.Z., aged 34, Polish, married at seventeen, and the mother of two children. The family history was negative for diabetes, cardiovascular disease and all forms of vasomotor dystrophies.

Personal history.—She emigrated to Canada in 1931. Her habits were normal. She denied all previous major infections. The history of the various systems was equally negative, and we can briefly state that until the onset of the present illness she never knew what a sick day was.

Present illness.—This began in the winter of 1934, when she began to suffer with coldness of the index and middle fingers of the right hand, which on exposure to the weather would turn blue and tingle. On her return to the warmth of the house the affected fingers would gradually turn white, and after half an hour resume their normal colour. She also noticed that immersion in warm water would hasten the return of the colour to normal. Some weeks later the ring finger of the right hand also became involved. At first practically no pain was associated with these colour changes, although she noticed some time later that the ends of the fingers of both hands were becoming larger. Then the index, middle and ring fingers of the left hand presented similar changes on exposure to the cold, though not to such a marked degree. During the summer of 1934 she had not been troubled with the vasomotor disturbance. In November, 1934, the tip of the right middle finger became very painful and after soaking it for some time in hot water a small amount of whitish material was expressed from under the nail. This discharge continued for a few days, when it ceased, though the finger remained painful. About the middle of November the tip of the right index finger also became painful and the same kind of white material was expressed. More recently she had noted that the pulp of the tips of the index and middle fingers had become hard. While the pain was never severe enough to prevent her from sleeping she was unable to work with any comfort, and reported to the surgical outdoor clinic on January 2, 1935, where after a routine examination she was referred

to the medical outdoor clinic as a case of Raynaud's disease. In the meantime an x-ray plate had been taken of the fingers (see illustration).

After admission to the wards on January 3, 1935, she recalled that on two or three occasions the material discharged from the fingers contained some hard chalky granules slightly larger than the head of a pin.

Physical examination (January 3, 1935).—The patient was a well nourished woman, with a curious sallow complexion and a pinched, drawn appearance about the naso-labial folds. The conjunctivæ had a subicteroid tinge. The tongue was small and pointed and had a somewhat atrophic mucosa at the tip and edges. The thyroid gland was not palpable. The lungs were clear. The heart was not enlarged. The blood pressure was 130/90 m.m. There was no enlargement of the liver or of the spleen.

The hands presented a remarkable appearance. The terminal phalanges of all the fingers of both hands were uniformly swollen and had a dusky red colour. These changes were more noticeable in the fingers of the right hand. The skin was sweating and the finger tips felt hot. The tips of both index fingers were hard and the right index finger tip was tender. The nails of the right middle and index and left index fingers were a little grooved and irregular. There was no discoloration of the feet but they presented a distinct increase in the perspiration.

Our first impression was that the patient was suffering from Raynaud's disease, but we were surprised to see in the x-ray plates of the fingers two or three dense white areas in the subcutaneous tissues of the terminal phalanges (see illustration). We accordingly realized that further investigation was necessary. We then noted that the radial pulses were equal on the two sides, as were also the pulses of the dorsalis pedis. Sensation to touch and pain was very acute over the four extremities, and the reflexes, both in the uppers and lowers, were normal.

The urine examination did not reveal in the catheter specimen either albumin, sugar or casts. The blood Wassermann test was negative. The blood count showed no anaemia, but a slight leucopenia with an eosinophilia and an increased percentage of monocytes. The plasma phosphorus was 3.75 mg. per cent (normal 3 to 5 mg. per cent) and the serum calcium 9.2 mg. per cent (normal 9 to 11 mg. per cent). The fasting blood sugar was 0.095 per cent. A complete blood study on January 5th showed hgb., 93 per cent (H) — 15.8 g.; red blood cells, 5,820,000; leucocytes, 6,050; platelets, 116,000; reticulocytes, 0.5 per cent; red cell diameter, 7.6 microns; differential count—polymorphonuclears, 48 per cent; lymphocytes, 24 per cent; eosinophiles, 8 per cent; monocytes, 9 per cent; basophiles, 1 per cent; degenerate forms, 10 per cent. A basal metabolic rate of January 6th, was -5 per cent. The skin temperatures were studied by Dr. C. W. Fullerton, and were reported to be peculiar, as the fingers which were chiefly affected were warmer than the other fingers. In short, the reactions were not those commonly seen in the vasomotor neurosis of Raynaud. A check on the phosphorus and calcium of the plasma and serum gave somewhat similar figures to the original (3.15 and 10.5 mg. per cent).

A review of the films taken in the outdoor clinic on January 2nd and those of January 5th and 7th after her admission was presented as follows by Dr. E. M. Crawford of the x-ray department. "At the tip

* It was Dr. Howard's intention to bring out a monograph on this subject, and he had actually delivered a paper on it before the California Medical Association just preceding his untimely death in June, 1936. The present article has been prepared by friends from the material which he had gathered. Lack of space has necessitated much condensation and even elimination.

of the distal phalanges of the fingers of both hands one notes a loss of bone which involves the distal phalanges of the thumb, index, middle and ring fingers of the right hand, and the index, middle and ring fingers of the left hand. Associated with these changes are subcutaneous areas of calcification at the tips of these fingers. Throughout the distal portion of each terminal phalanx, one notes that the bone is definitely denser, and that the trabeculation in the marrow cavity tends to be obliterated by more compact bone. There is no loss of joint spacing of the interphalangeal and metacarpal joints, nor undue rarefaction of any of the bones of the hand or wrist. The compact bone of the cortex of the metacarpals appears to be increased. The above changes are not seen in any of the bones of the feet. The loss of bone in the terminal phalanges of the finger is seen in Raynaud's disease, scleroderma, and leprosy. The presence of subcutaneous calcified areas, however, is reported as being in favour of scleroderma. There is no evidence of

gland daily there was no appreciable improvement in the scleroderma or of the enlargement or discoloration of the fingers. On February 2nd the nail of the right middle finger was avulsed because of evidence of subungual infection. A few days later some material was expressed from the tip of the right index finger, which was again examined for crystals and on this occasion the fluid contained 10 mg. of calcium carbonate as proved by chemical analysis. While under observation in the ward on March 3rd and 4th, she had a vasomotor attack involving the fingers of the right hand, which became cold and blue from the tip of the finger to the first interphalangeal joint; the ring and middle fingers of the left hand were similarly involved. The colour disappeared quickly after immersion in warm water. Another attack was seen by me on March 4th. As the patient's general condition remained stationary and the local condition subsided she was eventually discharged from the wards, with the request to continue on the



calcification of the arteries." We felt certain by this time that we were dealing with a case of early scleroderma as suggested by the peculiar complexion and pinched expression about the face, the atypical vasomotor responses in the finger tips, and the peculiar blood picture with its eosinophilia of 9 per cent. A further study of the literature revealed the fact that similar pictures had been described in both Raynaud's disease and in scleroderma. We investigated the patient carefully for evidence of generalized scleroderma with partial success. The skin of the forehead was perhaps a little thick and dry and was pinched up with difficulty. There was a little thinning of the outer margin of both eyebrows. The axillary hair was sparse and the axillae were unusually dry. The skin over the thighs and lower legs was inelastic. On the other hand the skin of the feet was moist. There was apparent enlargement of the terminal phalanges of both great toes, though there was no corresponding colour change. The later blood counts revealed a persistence of the eosinophilia, which rose on January 16th to 12 per cent. A search for calcinosis of other regions, such as the feet, neck, shoulders, elbows and lung parenchyma, proved negative. In spite of the administration of thyroid extract, 5 gr. of the whole

thyroid extract medication in doses of one grain of desiccated extract (P. D. & Co.) daily on alternate weeks. She was to report to the medical outdoor clinic where her progress could be watched.

This case can be grouped under the rare, though now well recognized, syndrome of Thibierge and Weissenbach, who in 1911 described a similar case and reviewed 8 others from the world literature. Subsequently, Durham reported a case of his own and reviewed 13 other cases published since the original communication of Thibierge and Weissenbach. In 1933 Weissenbach and Basch were able to collect 46 cases from the literature and gave a very extensive review of the chief features of the syndrome. Subsequently, I have found some 5 or 6 other cases, thus making a total of 63.

My second case, though not so advanced as far as the scleroderma and calcinosis are concerned, is quite typical and presents another feature, namely, a destructive arthritis which has been recently observed in association with scleroderma by some of the French clinicians.

CASE 2

L.L., aged 45, female, domestic, was admitted to the Montreal General Hospital on June 3, 1935.

Complaints.—Sore, swollen finger joints for six or seven years; loss of weight and loss of appetite.

Family history.—Her father had died at the age of 40 years from heart disease, presumably rheumatic. Her mother was still alive and well at the age of 74 years. Five brothers and two sisters were alive and well. One brother had died at 24 from heart disease, presumably rheumatic. A maternal aunt had suffered from arthritis. There was no other familial predisposition.

Personal history.—The patient was born in London, Eng., where she resided until the age of 20, when she emigrated to Canada and had since lived here. She had worked as a maid until quite recently. Her habits were excellent. She did not abuse tea or coffee and did not use alcohol or tobacco. Of the common childhood diseases she recalls German measles only. She did admit that as a child she had growing pains, but never frank rheumatic fever. There had been no liability to head colds but the tonsils and adenoids were removed in 1924. She recalled an occasional mild chest pain, but had never had bronchitis or pneumonia. She had had rather frequent headaches but never had vertigo. She admitted occasional precordial pain with radiation to the left shoulder and down the left arm as far as the elbow joint. She had also noted frequent attacks of palpitation and fatigability, particularly since she has been a semi-invalid for the past year or two. She had had several of the teeth removed in the recent past because she thought they might cause her arthritis. The appetite had failed recently and she had been troubled with gaseous eructations. There had been no abdominal pain. The stools had become constipated since her activities had been restricted. Menses began at the age of 16 years, were always regular of the twenty-eight day type, but inclined to last for eight days, with some dysmenorrhœa. For the latter she finally had a dilatation of the cervix in 1917. She had had no dysuria or hæmaturia and denied both lues and gonorrhœa. Her maximum weight was 118 lbs., and she considered her average weight 110 lbs.; her recent weight was 102 lbs.

Present illness.—This began six years before her admission, when she first noted a curious roughening and scarring of the skin on the dorsum of the right foot. As her foot began to swell shortly afterwards she was referred by her family physician to the orthopædic outdoor clinic of the Montreal General Hospital, where she was told that she had some form of chronic arthritis, and was referred to the various special clinics for further study. Among others, she visited the dermatological clinic, where a diagnosis of localized scleroderma (morphœa) of the right foot was made. She also was referred to the dental clinic and a few of the teeth were removed.

She was able to carry on fairly well, but two years later she began to note swelling of the left index finger as well as stiffness and pain on movement. A few months later the right index finger became similarly affected and gradually the other fingers of both hands became involved. She was able, however, to carry on her work as a children's nurse until January, 1934, when the pain, especially in the feet,

became so marked as to force her to give up her occupation and take to bed. About January 1, 1935, the wrists, elbows and shoulders became painful and swollen. She then developed pain behind the knee joints. She continued to report to the orthopædic clinic, where she received Crowe's vaccine and other remedies without benefit. She was finally admitted to the medical wards for further observation and treatment.

Physical examination (June 4, 1935).—The patient was a thin English woman of about the stated age. Her face was small; the lips thin, though there was no definite sclerodermatous mask. The hair was fine and abundant and presented no premature graying. The eyebrows were a little thin. She wore glasses. The pupils were round and equal and reacted promptly to light. The tongue was clean. The surviving teeth were well preserved. The pharynx was clear. There were no palpable glands in neck, axillæ, groins or elsewhere. The thyroid gland was not palpably enlarged. The general nutrition was poor. The muscles were small, the subcutaneous fat, scant. *Thorax* was of flat feminine type and moved equally on the two sides; lungs normal.

The heart presented no undue pulsation. P.M.I. could be localized in the 5th interspace, 5.3 c.m. No undue shock or thrill. The relative cardiac dullness was diminished. The heart sounds were loud and clear; no murmurs. The pulse was 82, regular in force and rhythm. The brachial wall was barely palpable. Blood pressure 100/68.

The abdomen was rounded and symmetrical, without abnormality.

Joints.—The hands revealed some atrophy of the interossei, with typical fusiform swelling of the interphalangeal joints. There were no Heberden's nodes. The wrists, elbows and shoulder joints were not remarkable. The dorso-lumbar spines were free; hip joints clear. Both knee joints presented some limitation of movement but no apparent increase of fluid in the joint cavity and no thickening of the joint capsule.

Over the right ankle and dorsum of the foot one sees an area of thickened, shiny, inelastic skin which cannot be pinched between the fingers. The tarsus and metatarsus presented no gross deformity, but the toes, particularly the right little, were flexed and the latter over-rode the fourth toe. On the outer aspect of the right ankle joint was a small subcutaneous nodule. Our impression was that we were dealing with some chronic form of the degenerative arthritis with an associated scleroderma.

Laboratory investigation.—The catheter urine was negative for albumin, sugar, blood and casts, but contained an occasional pus cell. Many subsequent urinalyses were made with the same negative findings.

The blood revealed always a slight reduction of the hæmoglobin, ranging from 70 per cent (Hellige) to 52 per cent, while the red blood cells varied from a maximum of 4,850,000 to a minimum of 3,660,000. Further, the leucocytes ranged from 11,000 to 8,000, but the former high level followed a reaction from typhoid vaccine. The blood Wassermann test was negative to both antigens. The blood chemistry revealed a urea nitrogen of 11 mg. per cent; creatinine, 1.43 mg. per cent; uric acid 2.48 per cent; and a blood sugar of 0.090 per cent. The basal metabolic rate was minus one per cent on June 1st.

The nose and throat department could find no evidence of infection in the nose or the accessory sinuses. The dental clinic reported a satisfactory condition of the teeth, and later a gynecologist was consulted and he reported no lesion of the pelvic organs.

X-ray examination.—The x-rays proved of great interest, as from the very first we were struck with the presence at the head of the 5th metacarpal bone of two white opacities, the size of a pinhead and a similar one at the head of the first phalanx of the left thumb.

Further, there was a destructive arthritis of the proximal interphalangeal joint of the index finger and of the little finger of the left hand, with an area of destruction of the head of the metacarpal bone of the little finger. The other joints were clear but there was obvious increase in the calcium deposit of the upper third of both ulnæ and the lower third of both humeri. The upper half of both humeri showed definite generalized decalcification. The ankle joints were clear, but there was slight decalcification at the lower end of the fibulæ. These findings reminded one of the case previously reported, but it was decided to watch the case and to first give her a course of thyroid extract, which was begun on June 21st and after 50 grains had been taken it was discontinued, when she was given a course of ovarian extract in the form of B. & W's tabloid varium, 5 grains twice a day. By July 20th she had completed this course and had received as well increasing doses of typhoid vaccine without evidence of any improvement. She was accordingly started on Parke Davis & Co.'s parathyroid extract, grain $\frac{1}{4}$, twice a day. On July 30th the typhoid vaccine was discontinued and she was given in addition to the glandular therapy half a gram of calcium ortho-iodoxybenzoate three times a day. She continued, however, to complain of her joints, particularly the right knee and right ankle joint, which became swollen as well as painful and tender. On August 15th the corrected sedimentation velocity rate was somewhat elevated, being 0.6 mm. per minute instead of the upper limit of normal of 0.38. By September 6th we could see no appreciable change in the patient's condition, in spite of the many and various treatments instituted. No new areas of scleroderma had appeared, though there were a few white spots over the forearm and about the wrist joint, somewhat suggestive of scleroderma guttata, and the face was beginning to look thinner and more pinched. Further, there was some discoloration of the finger nail of the right index finger, as well as striking nutritional changes of the nail of the right index and the nails of both thumbs, ring and little fingers, such as are commonly seen in scleroderma. There was no change to be seen in the calcium deposits around the phalanges as previously described. She was accordingly started on more thyroid extract and given some more typhoid vaccine, this time intravenously. Of course following the latter there would be a chill and a rise in temperature, but otherwise the course was afebrile. By November 13th she had finished the second course of thyroid extract of 125 grains and we began the use of Merck's parathormone, 2 units daily, until she had received 100 units by December 15th. In spite of this treatment the arthritis persisted, and she began to note stiffness in the neck, with tenderness and pains in the various joints previously affected, as shoulders, wrists, elbows, knees and ankles. By January 1, 1936, she was anxious to try once more the thyroid extract, which she maintained gave her more relief than any other therapeutic procedure to which she had been submitted. Accordingly, as she had completed her second course of parathormone on January 3rd she was again started on the thyroid extract on January 4th. On January 13th for the first time her blood calcium was estimated at 9.8 mg. per 100 c.c. a normal level and a plasma phosphorus of 3.33 mg. per cent, while the blood uric acid was 3.63 mg. per cent. On the same date her sedimentation rate was still elevated, 0.95 mm. per minute.

During January and February there was no appreciable change in her condition. There had been periods of good and periods of bad days. She remained afebrile. On February 28, 1936 she started her third course of parathormone, when her blood calcium was again found to be 10.9 while the phosphorus was 3.3 mg. per cent. About this time she showed some urticaria and as one brother had hay-fever and asthma, her skin sensitivity to various foreign proteins, including foods and various tests, was tried. All proved negative except for a very slight reaction to silk. On March 16th she began another

course of thyroid extract, 3 grains daily, after the completion of which on April 3rd she had a fourth course of parathormone.

On April 17th her serum calcium was 9.1 and her serum phosphorus 2.5 mg. per cent. On April 20th the serum phosphatase by the King and Armstrong method revealed 5 units. The serum calcium 8.9 mg. per cent and the phosphorus 4.05 mg. per cent. The sedimentation velocity rate had fallen to 0.5 mm.

CLINICAL CLASSIFICATION OF THE SYNDROME

Basch in 1932 and Weissenbach *et al.* in their paper of 1933 divided the 46 cases available for study into the following clinical groups.

I. *The calcareous concretions of diffuse scleroderma*: A. progressive scleroderma from a localized beginning (more often sclerodactylia); B. oedematous scleroderma (developing towards chronicity).

II. *The calcareous concretions of circumscribed scleroderma*: A. scleroderma en plaque (morphœa); B. scleroderma en bande.

III. *Associated forms*: A. rheumatic scleroderma; B. latent tetany, with or without cataract.

I. GENERALIZED SCLERODERMA

A. *Calcareous concretions of scleroderma progressing from an onset with sclerodactylia*.—Of the 27 cases of this group 26 occurred in females. The concretions appeared in mid-life, between the age of 17 and 69 years, and usually at the time of the menopause. They were always preceded, except in 2 of the 27 cases, by a Raynaud's syndrome as manifested by chilblains, acrocyanosis, paræsthesiæ, local syncope, followed by asphyxia and pain chiefly affecting the upper extremities. A less common mode of onset is a fibrous periartthritis, which was observed in 5 cases. The painful swelling of the joints progresses without acute exacerbation but with moderate fever and was often considered at first as a manifestation of acute articular rheumatism.

The scleroderma is first manifested by the gradual appearance of sclerodactylia. Rarely does scleroderma first appear in the face. In either event the scleroderma progresses and pigmentation of the skin (10 cases) and telangiectases (5 cases) develop. The calcareous concretions appear insidiously and without pain in the pulp of the fingers, as hard subcutaneous nodules more or less adherent to the overlying skin but not to the deeper tissues. Gradually the overlying skin becomes thinned out, permitting one to recognize a yellowish or whitish

colour to the nodule. Finally, ulceration occurs, resulting in the discharge of a creamy material or even calcareous particles as in our own case. The concretions were localized in the fingers in 17 cases, and were found chiefly on the palmar surface of the pulp of the fingers, with a liability to extend to the proximal phalanges. In 7 cases they were found over the olecranon, but usually only subsequent to their appearance in the fingers. They appear more frequently in the forearm than in the upper arm. While much rarer in the lower extremities, they have been noted six times about the patella and elsewhere in the lower extremities (in order of frequency, about the big toe, the thigh and the leg). The face is rarely affected (three cases) and the trunk only exceptionally (one case).

The concretions are situated in the sclerotic zones of the skin or subcutaneous tissue in every case which has been studied with care. They are situated in the lower layer of the skin or in the subcutaneous tissue. The nodules consist most commonly of solid concretions of stony hardness and of varying forms and sizes, ranging from the head of a pin or a grain of millet to the size of a pea or a hazel nut. Rarely, they form plaques or masses which may reach 20 cm. in diameter. In a few cases the calcareous salts consisted of a semi-liquid creamy fluid. Spontaneous extrusion is the rule, usually gradually and silently but sometimes associated with acute pseudo-inflammatory reaction, as pain, redness of the skin and ulceration. More frequently the infection is secondary to either the spontaneous or artificial expulsion of the calcareous material. Spontaneous resorption is exceptional. The chemical composition of the concretion consists partly of organic and partly of mineral material in varying proportions, depending upon the type of the precipitation; in the case of the small superficial nodules the organic matter is in excess, while in the creamy fluid and in the deep concretions the proportion of mineral matter forms from 1 to 87 per cent of the total, and consists chiefly of calcium carbonate and calcium phosphate, with traces of fluorin, sulphur, magnesium and an appreciable amount of iron. The organic matter is made up of albuminoids, proteins, and cholesterol. In short, the nodules follow the general law of the formation of gouty tophi. Five cases revealed a muscular atrophy with interstitial sclerosis, in 2 of which

there was, in addition, a sclerosis of the tendons with restriction of movement. Electric examination shows a diminished response to both the galvanic and faradic currents. In only 6 of 20 cases studied by x-ray was there noted a decalcification of the phalanges of the fingers and sometimes of the distal ends of the metacarpal bones. These bony changes are always associated with a marked sclerodactylia. In this group endocrine disturbances are common, as suggested by the frequency of the syndrome in the female. Ovarian and thyroid troubles were found in 14 cases; in 7 there was a hypofunction of the ovarian secretion, as shown by amenorrhœa, by the late appearance of puberty, irregularity of menses, sterility, hypoplasia of the mammæ, and by the tendency for scleroderma and calcinosis to appear after the menopause.

The thyroid gland was enlarged or diminished in size in 9 cases, associated with chilliness, loss of hair and alteration in the basal metabolic rate. The latter showed a slight decrease in 3 cases and a marked increase in 3 other cases, ranging from plus 30 to plus 40 per cent. The hypophysis was abnormal in 3 cases. In 2 there was calcification and in a third there was an enlargement of the sella turcica. In 3 other cases in which the latter was examined, it was of normal size. Changes in the parathyroid glands are rarer. Milian *et al.* reported a tumour of one parathyroid gland and hypertrophy of the other. Two cases showed a slight Chvostek phenomenon and one other was associated with cataract (Rothmund's syndrome).

B. Calcareous concretions of the œdematous scleroderma.—Eleven of the 46 cases can be placed in this group (Dietschy). Nine of these were females and 2 were males. The age period is, however, different from the previous group as it is a disease of youth, even of infancy. The average age of onset was between the eighth and the fifteenth year. The onset was acute or sub-acute in 7 cases. When acute there is a sudden onset of fever and chills followed by a localized or a generalized œdematous infiltration of the skin. This may be associated with painful swelling of the joints resembling acute articular rheumatism or infectious arthritis. There is general lassitude, stiffness of the joints, and even immobilization of the vertebral column. The scleroderma is of the diffuse type, but is particularly noted over the trunk, neck and

upper extremities. Atrophy of the skin follows with the appearance of a lemon colour and pigmentation as well as telangiectases in different regions of the body (4 cases). There may be a generalized muscular atrophy with contracture of the joints as in Dietschy's case. The muscles, and even the tendons and aponeuroses may become sclerosed. Calcification occurs in the areas most affected by the scleroderma, whether they be deep or superficial. The nodules appear more often in the upper than in the lower extremities; the other sites in order of frequency are the pelvic and scapular regions and the abdominal walls. They are never superficial but vary in size from a lentil to a tangerine, and may form a cuirasse as in the cases reported by Krause and Trappe and by von Gaza. The extrusion of calcium salts is much less frequent, but occurred in 5 cases of this group. The muscles reveal a diminished response to both the galvanic and faradic currents. The skeleton is often decalcified, as was shown by x-rays in 4 out of 6 cases in which skiagrams were taken. The decalcification was especially marked in the cases of von Gaza and of Paiseau. The endocrine glands are affected, as illustrated by the incidence of infantilism, exophthalmos and enlargement of the thyroid gland. The prognosis is more serious in this type than in the preceding one. Death usually results from progressive cachexia, some secondary infection, or tuberculosis.

II. THE CALCAREOUS CONCRETIONS OF THE CIRCUMSCRIBED SCLERODERMA

A. *Scleroderma en plaque* (Morphœa).—The mere fact that there were 4 cases of this type shows that it is not a rarity. The cutaneous lesions are always primary. The site is usually the face, particularly over the cheeks and such exposed regions as the neck and arms. The legs or feet may also be involved. When the face is affected it sometimes reveals a violet colour or is surrounded by a lilac ring (Lortat-Jacob). The concretions appear in the middle of the plaques and only exceptionally occur in the healthy skin (Hoffmann). They are usually subcutaneous, but may also be intracutaneous. Eruption of calcareous material occurred in at least two of the cases with resulting ulceration but without a tendency to scar formation. In this small group of cases there were no muscular or skeletal lesions. Evidences of disturbance of the en-

docrine glands occur, such as obesity, Chvostek sign, diabetes, etc.

B. *Scleroderma en bande*.—In the series of 46 cases Basch found no pure case but in 2 cases of progressive scleroderma there was also present the horizontal band of sclerosis extending from one sternocleidomastoid region to the other (Bertolotti and Pernet). In one of these cases a band on the anterior surface of the wrist was also found.

III. ASSOCIATED FORMS

A. *Rheumatic scleroderma and calcareous concretions*.—Five such cases have been recorded, Hunter (1913); Langmead (1912 to 1919); Paiseau (1930); Milian, Perin, Horowitz (1930); Weissenbach, Truchot, Francon and Laudat. Our second case makes the sixth. It must be admitted that the term rheumatism is used in its broader sense. As has been shown articular symptoms may occur with the onset of the syndrome of Thibierge and Weissenbach, but apart from this an arthritis may occur in several forms—(1) deforming rheumatism, (Paiseau's case) and osteoarthritis (Milian's case); (2) peri-arthritis fibrosa, (a) with calcification in the course of scleroderma, (cases of Hunter and Neuwirth), (b) primary peri-arthritis fibrosa with secondary calcinosis and late appearance of scleroderma (cases of Weissenbach, Truchot, Francon and Laudat); (3) alveolar arthritis due to resorption or dry pyorrhœa, (two of the personal cases of Weissenbach and Basch). The existence of similar trophic troubles in Raynaud's disease, scleroderma and chronic arthritis is a link between them, and, according to Lafitte and May, constitutes an argument in favour of a true sympathetic origin.

B. *Latent tetany with or without cataract*.—The association of the Thibierge-Weissenbach syndrome with symptoms formerly considered a result of hypoparathyroidism is of considerable interest. The existence of Chvostek's sign, (Lereboullet), hypocalcæmia, (Garcin), and even cataract, the syndrome of Rothmund (Mamou), are illustrations of this group. It further shows the difficulty of interpreting the existing rôle of the endocrine gland in the pathogenesis of this syndrome. Mamou, contrasting the syndrome of Rothmund with the syndrome of Thibierge and Weissenbach, offers the hypothesis that the former (scleroderma with

cataract and tetany) is due to hypoparathyroidism, and the latter (scleroderma with calcification) is due to hyperparathyroidism.

PATHOGENESIS

According to Durham there are several mechanisms by which calcinosis might develop in scleroderma. First, as a result of a parathyroid dysfunction; secondly, as part of a metastatic calcification; thirdly, by simple chemical precipitation, and, fourthly, by means of a physico-chemical disturbance in which colloidal proteins play a rôle.

Basch discussed the pathogenesis of this syndrome under three main theories: (1) diathesis; (2) local factors, and (3) synthesis. *The theory of diathesis* assumes that calcinosis is a consequence of a general humoral disturbance dependent upon three different factors. The calcinosis may be due to hypercalcaemia of osseous origin, as originally suggested by Virchow and more recently supported by Wells and Schultze. There is associated with the initial osseous affection a renal lesion which prevents the elimination of calcium and its consequent deposition in certain tissues and organs of the body. The main argument in favour of this theory is the frequency of decalcification of the skeleton observed in all severe cases of calcinosis. This decalcification is not constant, and in other conditions, as osteomalacia, chronic rheumatism and pregnancy, in which manifest osseous decalcification occurs, calcinosis of the tissues is rare. However, decalcification of bone is seldom found and renal damage was present only once in the 46 cases investigated by Weissenbach and his associates.

Is the calcinosis due to an excessive ingestion of calcium or a simple retention of calcium? A constant hypercalcaemia is not found, as in the majority of the cases the total calcium of the blood is normal or below normal; only twice was it above normal on the first examination. These observers conclude that the theory of excessive calcium in the blood is contrary to the clinical facts. It appears therefore, generally accepted that the precipitation of calcium in the tissues is not due to an excessive calcium in the blood.

That a disturbance of metabolism results in some qualitative or quantitative alteration of the serum other than of the calcium has been

suggested as (a) an excess of phosphorus; (b) a dissociation of the colloids of the blood, and (c) a disturbance of the acid-base equilibrium. The authors admit that both clinically and experimentally these may possibly play a rôle in the precipitation of calcium salts, but they are not constant clinical findings, and there is a disagreement and even a contradiction in the analytical results so that it is impossible to draw any conclusion concerning the element responsible.

2. *The theory of local factors.*—This theory assigns the precipitation of calcium to a local alteration of the connective tissue conferring a special physico-chemical affinity for calcium salts. The adherents of this theory offer the following arguments in its support. (a) Proof of the existence of local lesions preceding the precipitation of calcium salts clinically, experimentally and pathologically. (b) The mechanism of local vascular factors consists of (1) an increase of certain elements as calcium, phosphorus and the proteins, in the interstitial lymph; (2) a modification of the tissue pH or a state of alkalosis; and (3) the rôle of the connective tissue. The endocrine glands, ovaries, testes, thyroid, parathyroid and hypophysis, possibly play a direct part in the precipitation of calcium salts as well as in the pathogenesis of scleroderma. Basch favours the parathyroid glands for this double rôle. In 1929 the parathyroid origin of scleroderma was suggested by the work of Pautrier and Zarn. In 1931 Leriche tried to prove this hypothesis by the removal of one parathyroid in cases of scleroderma, with suggestive results, as the disease retrograded. In 1932 Selye published his experimental scleroderma in 20 per cent of animals injected with parathormone. In 1933 Shelling, Ashes and Jackson confirmed these results. Finally in 1935 Leriche, Jung and Suregya injected a young pig and several series of young rats with Collip's parathormone and with Byla's parathyrone, which in several days revealed, cessation of growth, emaciation, thickening of the skin, loss of hair, increased calcium content (to 3 or 4 times the normal control). Histologically, there was infiltration and later destruction of the dermis with calcareous infiltration, and in the later stages a marked connective-tissue proliferation in the dermis with atrophy of the dermis. These experiments lend considerable support to

the theory of a parathyroid origin of scleroderma. In a later publication Leriche and Jung concluded, from the study of some 20 cases, that scleroderma is a cutaneous form of chronic hyperparathyroidism. There are then stages of hyperparathyroidism, osteolysis and cutaneous atrophy.

3. *The theory of synthesis.*—Hunter concludes that in the pathogenesis of the calcium concretions of scleroderma as well as in the related syndromes of Raynaud and the cutaneous atrophy of certain chronic forms of rheumatism, the essential factor lies in the alteration of the tissues which have an elective affinity for calcium salts. The coexistence of both local and general disorders seems to offer the optimal conditions for the precipitation of calcium in the skin and subcutaneous tissues.

Hunter in 1913 wrote, "Scleroderma is apparently a chronic interstitial inflammation of the skin and it is probably dependent on a chronic local arthritis". The calcinosis is "secondary to the fibrotic changes in the skin, and thus analogous to the calcareous deposits in the sclerosed valves of chronic endocarditis or the cicatrices of old tuberculous lesions in the lungs". The calcification would, therefore, be a terminal phase of the fibrous, an alteration in the vitality of the sclerosed tissue determining the deposit of the lime salts. This is the view favoured by Thibierge and Weissenbach in 1911.

PATHOLOGY

A bacteriological study of the nodules has been practised in only a few cases, and has proved negative in both anaerobic and aerobic culture media. Direct smears of the material stained by Gram, Ziehl-Neilsen and by thionin have revealed no bacteria. Even guinea-pig inoculation has proved negative.

The histological study has yielded more positive findings, and has shown that calcification may attack different elements of the connective tissue, but particularly the collagen and elastic tissue fibres. The essential histological changes consist of hypertrophy of the pre-existing connective-tissue bundles followed by pressure on the vessels and epidermal structures. There is a considerable amount of perivascular and periglandular infiltration with lymphoid cells, and the papillæ are at first swollen but later shrunken and flattened. The elastic tissue may be slightly increased in amount. The calcifica-

tion of the collagen fibres has been reported in eight cases (Thibierge and Weissenbach, Lewandowsky, Stradiotti, Durham, Oehme, Thibierge-Spillmann and Weissenbach, Pollitzer and Lostat-Jacob, Fernet and Bureau). In the earliest stage, before there is clinical evidence of calcinosis, one can recognize histologically two types of lesions: (1) those of the diffuse sclerosis of the skin, and (2) a microscopic precipitation of calcium salts in the deeper layers of the skin, either as calcareous granules interlarding the connective tissue, or as crystallized bodies isolated or grouped in small masses. In the later stages macroscopic study reveals a tumour formed by dense fibroid tissue, whitish yellow in colour, and without a definite boundary from the true skin. This tissue is infiltrated with little hard white granules, varying in size from the head of a pin to a grain of hemp. Microscopically the central portion is made up of an amorphous substance which stains intensely blue with hæmatoxylin-eosin and polychrome blue, and gray with Van Gieson. At the periphery the connective tissue is perfectly homogeneous, with limited spaces filled with little collections of material of varying sizes giving all the reactions of the central mass. It is in this zone that one finds the calcareous concretions and the epithelioid and giant cells. In the neighbourhood of the giant cells one finds a rare mononuclear cell with acidophilic protoplasm, and an oval nucleus resembling the so-called epithelioid cell. In the third and last stage the deep-lying concretions become encysted in a dense fibrous wall, while the superficial ones are discharged by ulceration of the skin. The calcification of the elastic fibres is less commonly observed though it was present in two cases (von Gaza and Bruusgaard). The fibres first undergo degeneration, as shown by swelling, fragmentation, etc., and then become impregnated with calcium salts. The rarity of the elastic fibre calcinosis corresponds to the rarity of the degeneration of elastine in scleroderma. The muscular lesions consist of a hyperplasia of the interstitial connective tissue with hyaline degeneration (Oehme). There is a secondary atrophy of the muscular fibres from the enormous connective-tissue hyperplasia which is associated with calcareous infiltration of the hyalinized tissue in the form of granules or masses of calcium salts as shown by the silver stain. There results also

some perivascular round-celled inflammatory reaction (Dietschy, Krause and Trappe, von Gaza, Oehme). Secondary ossification of the calcified areas is rare and was observed only once (Pollitzer). In this case the author noted typical osteoblasts disposed about the periphery of a plaque of calcium salts, but without any outline of the lamellar structure of normal ossification.

SYMPTOMATOLOGY

The general nutrition usually suffers to some degree. In the aortic and generalized calcinosis emaciation may be extreme. The skin may be ruddy or pale, but often shows the generalized or localized changes of scleroderma. Pigmentation of the skin occurred in at least 10 of our series. It may be thin or thick, wet or dry. The peculiar vasomotor phenomena of Raynaud's disease are often present and may initiate the onset of the disease. They are however never quite typical and seldom if ever lead to gangrene. Gritty, chalky material is present in which crystals of calcium carbonate or phosphate or both are recognized. Arthritis may be present as in our second case, and has been described in 5 other cases in the literature (Hunter; Langmead; Parisseau-Schaeffer and Scherer; Milian, Perin, Horowitz and Weissenbach, Truchot, Francon, Landat). It may occur in several forms—(1) deforming rheumatism, with or without Osler arthritis; (2) periartthritis fibrosa, (a) with calcification in the course of scleroderma, (b) as a primary periartthritis fibrosa with secondary calcinosis.

DIAGNOSIS

The diagnosis should not be difficult, once the existence of the syndrome is realized. One's suspicions should be aroused in the case of any patient with scleroderma or with obscure rheumatic features, and careful x-ray studies of the affected areas made. The following conditions of course have to be excluded.

1. *The uratic tophi of true gout*.—Here the age of the patient, as well as his clinical history, and the study of the blood uric acid, and, more particularly, of the chemistry of the tophi will make recognition easy.

2. *Calcareous concretions without scleroderma*.—One finds in the medical literature under the term "Calcinosis" a number of conditions in which calcium deposits are found in the skin. These are (a) calcified cutaneous tumours such

as the calcified epithelioma of Malherbe, fibromata, cysts and sarcomata; (b) phleboliths in subcutaneous varicosities of the legs; (c) the subcutaneous stony tumours of Poirier; and (d) true cutaneous osteomata.

3. *Cutaneous concretions of Raynaud's disease*.—Several of the cases considered by the reviewer as scleroderma have been reported under the title of Raynaud's disease. Our own case at first was labelled thus, but altogether apart from this, several cases, some 20 at least, have appeared in the literature in recent years in which only the diagnosis of Raynaud's disease could be made in spite of the presence of cutaneous concretions, (Garcin, Tamalzkia). The appearance of the calcareous concretions seems to coincide with crises of local asphyxia (Weissenbach, Vignal and Guillaumin, Fernet and Naham).

In the first place, without a biopsy, the absence of recognizable scleroderma does not permit one to assume the absence of pericellular lesions of sclerosis of the connective tissue and of neighbouring degenerative colloid alterations. In the second place, one knows how frequently after several crises of Raynaud's disease, slight cutaneous alterations quite distinct from true scleroderma are followed later by cutaneous atrophy rather than condensation of the subcutaneous tissue. Raynaud's syndrome, cutaneous atrophy, and sclerodactylia follow so insensibly that very often the patients do not recognize the change in their skin. It is not possible then in some cases to distinguish between the two conditions—Raynaud's and scleroderma—even when calcinosis exists. Basch accordingly considers it an argument in favour of their close relationship both from the etiological and pathogenetic point of view.

4. In the rare condition of *atrophic acrodermatitis* Jessner noted the presence of calcareous concretions in one case. Clinically, acrodermatitis is readily distinguished from scleroderma by its predominance in the male sex, its first appearance on the dorsal surface of the hands and feet and not on the fingers, and the combination of bands and sheets of erythema and atrophy whose colour varies from pale rose to a violet red. However, the frequent association of true circumscribed scleroderma and chronic dermatitis (in 60 per cent according to Pautrier), on the one hand, and the possible

transformation of true scleroderma into acrodermatitis, on the other, make the diagnosis most difficult, especially when calcinosis may occur in either condition.

In a case of *atrophic reticular poikiloderma* calcification of the skin was reported by Glück in 1913, and seven years later the same case was described by Lemanczyk under the title of "interstitial calcinosis". The cutaneous lesions had then largely subsided while the calcareous nodules had reached a considerable size. Here, theoretically, the diagnosis is easy, poikiloderma with its pigmented network of varicosities and its white meshes of skin in no way resembles scleroderma. Nevertheless, the case of Perges and Elijat was at first diagnosed "atrophic sclerosis", and Jacob's case was mistaken for scleroderma, according to Jadassohn (1912).

Of the *macular atrophies* one finds a case recently reported by Cavallucci under the title "Atrophie maculaire idiopathique de la peau avec concretion calcaires sous-cutanées symétriques", which bears a more striking resemblance to morphœa than to the generalized types of scleroderma. In short, one can say that the differential diagnosis of calcareous concretions of cutaneous atrophy from those of scleroderma depends rather upon the recognition of the morphological aspects of each condition, than a separation of distinct fundamental differences between them.

5. *Myositis ossificans*.—This rare condition has to be distinguished from the œdematous type of scleroderma with muscular calcinosis, according to Krause and Trappe. Myositis ossificans affects young subjects, runs a chronic or subacute course manifested by intramuscular tumours, at first mealy and then harder, in the midst of areas of œdema which spread rapidly. The muscular lesion affects first the muscles of the neck and back, then those of the extremities, eventually leading to complete ankylosis, and finally to death. One can readily confuse the

microdactylia, considered as pathognomic of myositis ossificans by many writers, with sclerodactylia or scleroderma. However, myositis ossificans has a predilection for boys, the muscles of the trunk are first and most intensely affected, the skin remains free, and there is always a fatal outcome.

TREATMENT

A word as to treatment. In the first group it is fair to state that the prognosis is good and treatment of the scleroderma as a rule suffices. Proper hygiene, as fresh air, daily exercise, and avoidance of exposure to cold should be enforced. Kennedy (1929) has reported decrease in the cutaneous lesion from the protracted use of a ketogenic diet (1932). Vasomotor dilatation may be procured by the hypodermic or intramuscular administration of acetylcholine, insulin, pancreatic extract and pilocarpine in appropriate dosage. Iodine in combination with thiosinamine and phosphoric acid may improve the general health of the patient, but will not prevent an extension of the calcinosis. There is, therefore, a tendency in recent years to recommend glandular therapy by the oral, subcutaneous and intravenous routes. Thyroid, ovarian, hypophyseal and pluriglandular extracts have been tried, but with little or no effect upon the calcinosis. In a small group of cases surgical removal of the diseased sex glands or of the thyroid, and more recently of the parathyroid glands, has been tried with more or less success. Leriche and others have reported remarkable improvement following periarterial sympathectomy in the early stages of the discrete form of scleroderma with calcinosis. Local symptomatic treatment by excision of the calcareous nodules, drainage of infected areas, and by electrolysis is justifiable for the relief of pain.

The very extensive bibliography prepared for this article by the author can be had on application to the *Journal*.

PARAFFIN FOR LOCAL HEAT.—F. Krusen describes a method of using a simple paraffin bath in districts where electricity is not available for the application of local heat. The use of hot towels, hot salt bags, or hot fomentations is often unsatisfactory, and a simple method of applying heat is described. About eight pounds of paraffin are placed in the inner pan of a 1½-gallon double boiler, the outer pan being filled with water and heated on a stove until the paraffin has reached melting-point. It is then allowed to cool to 75° C. A clean paint brush is then immersed in the melted paraf-

fin and the part to be treated is painted with about a dozen coats of liquid paraffin. This hardens and retains its heat for about twenty minutes, when it can be lifted off in a single sheet and returned to the boiler for subsequent use. Massage may be applied immediately after removal of the paraffin. Applications of warm paraffin are particularly indicated in the treatment of arthritis, fibrositis, sprains, stiffness of joints and muscles, or in the treatment of fractures after bony union has been established.—*Proc. Mayo Clin.*, February 3, 1937, p. 73. Abs. in *Brit. M. J.*

ASCORBIC ACID (VITAMIN C) TREATMENT OF WHOOPING COUGH*

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WHOOPING cough is an almost universal infectious disease, with its greatest infectivity in pre-school and school children. While some protection has been afforded against it by vaccination, treatment of the active disease has not progressed as has treatment of other infectious diseases such as scarlet fever and diphtheria. Madsen¹ reports that, of 1,842 vaccinated children, about 25 per cent escaped infection, while of 446 non-vaccinated children less than 2 per cent escaped. This decided improvement warrants the use of vaccines, but still leaves the infected child confronted with some weeks of unpleasantness and a not inconsiderable mortality rate. According to Tice,² in the registration area of the United States there were 7,518 deaths in 1934. In the years 1932-34 there were 45,755 cases of whooping cough reported to the Dominion Bureau of Vital Statistics, with 1,982 deaths. Of the fatal cases over 50 per cent occur in the first year of life. The non-fatal cases undergo a most disagreeable experience and lose considerable time from studies, in the case of the school-child. The disease is characterized by spasmodic coughing and vomiting, and this spasmodic or paroxysmal stage persists for weeks. How this paroxysmal stage originates, and why it should be so prolonged, has always intrigued investigators, and various hypotheses have been put forward. Among them is one suggested by Brown,³ that a neurotropic toxin elaborated by the bacillus in the early catarrhal stage affects the vagus and respiratory centres and possibly the sensory nerve-endings in the upper respiratory mucosa. Fixation of this toxin in nervous tissue would explain the comparative failure of vaccines or convalescent serum to influence the course of the disease unless given in the incubation period or early in the catarrhal stage. Both exo- and endotoxins have been obtained from the Bordet-Gengou bacillus.

Ascorbic acid has been investigated by

several workers from the standpoint of its detoxicating action. Grootton and Bezsonoff⁴ record the results of mixing diphtheria toxin and ascorbic acid, incubating very briefly, and injecting the mixture into guinea-pigs. Unneutralized ascorbic acid completely destroyed the toxic action, but this effect was one of pH and not a specific effect. Ascorbic acid neutralized with soda and mixed with the toxin so altered its potency that, of four guinea-pigs receiving 4 M.L.D. of toxin each, one survived and the others died respectively on the 4th, 6th, and 9th day. Controls injected with 4 M.L.D. each of unaltered toxin all died on the 2nd day. These workers, in the same paper, tested the actual bactericidal action of ascorbic acid against various bacteria by adding varying amounts of the acid to the culture medium, bringing the mixture to a pH of 7.0, and inoculating with such organisms as staphylococcus, streptococcus, gonococcus, typhosus, Bordet-Gengou, etc. With 0.5 per cent ascorbic acid mixtures only the gonococcus and Bordet-Gengou bacillus were inhibited, as compared with controls. The gonococcus grew readily in a 0.2 per cent mixture. In a percentage of 0.008, ascorbic acid inhibited the growth of the Bordet-Gengou bacillus. Glacial acetic acid added to the culture medium in corresponding amounts, and then neutralized, failed to affect the growth of this bacillus.

Woringer and Sala⁵ reported 4 cases of whooping cough complicated by scurvy occurring among a series of infants treated in their clinic. No scurvy appeared among the other children, although all were on exactly the same dietary regimen. They suggest that vitamin C is an essential part of the body's defence against the Bordet-Gengou bacillus, and that excessive demands made in the presence of such an infection may so deplete the vitamin stores of the tissues as to lead to the clinical condition of scurvy.

Gander and Niederberger⁶ and Hochwald⁷ report the use of ascorbic acid in the treatment of pneumonias. Pneumonia cases showed con-

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sistently a deficit in vitamin C. Administration of the vitamin produced an effect comparable with that of specific serum. The pulse and temperature subsided by crisis when the avitaminosis was completely relieved, as shown by beginning urinary excretion of the ascorbic acid. When small doses of ascorbic acid were given, the saturation point for the vitamin was reached slowly, and no clinical improvement was shown until this point was reached.

Various investigators^{8, 9, 10} have shown that the tissues of normal children and young animals contain more vitamin C than those of normal older subjects, and that the saturation point, as judged by beginning urinary excretion, is attained in young subjects only by much larger doses than relative weights would indicate. This suggests a greater need of vitamin C by young animals, and so a greater storage of it in the presence of an ample supply.

From this evidence, ascorbic acid seemed to have possibilities in the treatment of whooping cough, and one of us (B.M.U.) has been using

it in practice for the last two months or so. To date, we can report 9 cases, and 1 from another practitioner.* In each case, diagnosis was made from a history of contact with known cases together with personal observation of the typical cough, vomiting and nocturnal paroxysms. Cough plates or serological tests were not used in this preliminary investigation. Condensed case reports follow.

DISCUSSION

The short series of cases presented is too small to draw any statistical conclusions, but one fact stands out. Ascorbic acid has a definite effect in shortening the period of paroxysms from a matter of weeks to a matter of days. We have not checked by cough plates or otherwise in this preliminary work to see whether the infectivity subsides simultaneously with the spasmodic symptoms, but are continuing with a larger series of cases in which these and other tests will be employed.

* Case 4. We are indebted to Dr. C. H. A. Walton for details of this case.

TABLE

Case	Age (years)	Sex	Contact	Duration of Symptoms	Treatment	Results
1 R.T.	6	M	School	6 weeks—typical	150 mg. per day	7 days—cough reduced markedly 10 days—cough disappeared
2 C.H.	1½	M	Unknown Temperature 102 F. Bronchopneumonia when seen	3 weeks—typical 10 days "fever" at home	inhalations sinapisms expectorants } 3 days 175 mg. daily—11 dys.	No effect 7 days—temperature normal, cough reduced 14 days—cough disappeared
3 M.C.	12	M	School	10 days—typical	200 mg. daily	6 days—cough reduced 13 days—only occasional night coughs 15 days—all cough absent
4 J.P.	6	F	School	over 4 weeks— typical	200 mg. daily	3 days—cough less, no vomiting 7 days—occasional cough
5 B.O.	2½	M	Known case	2 weeks—typical	250 mg. daily	5 days—cough disappeared
6 H.F.	7	M	School	2 weeks—typical	375 mg. daily	4 days—cough less 9 days—night cough only 11 days—all cough absent
7 E.H.	22		Maid Child in house had whooping cough	4 dys., paroxysmal cough, vomited once, no whooping	500 mg. daily—3 days 125 mg. daily	4 days—cough less, no vomiting 6 days—coughed only once in 2 days 11 days—cough absent
8 B.P.	4	M	Known case	10 days—typical	500 mg. daily—4 days 250 mg. daily—4 days	5 days—cough disappeared
9 M.W.	6½	F	School	2 weeks—typical	500 mg. daily—4 days 250 mg. daily—5 days	4 days—cough reduced 7 days—coughed once in 24 hours 9 days—cough disappeared
10 W. C.	4½	F	Sister (Case 9)	1 week—typical	500 mg. daily—4 days 250 mg. daily—5 days	Same as for Case 9

The dosages used have been empirical, with a tendency to use larger doses early in the disease as our experience of its effects progressed. The acid is available at reasonable prices, and the danger of overdosage seems negligible. Animals have received 2,000 times their estimated requirements without any deleterious effects. Any excess is excreted by the kidneys.

CONCLUSIONS

1. A method has been described for the treatment of whooping cough by ascorbic acid (vitamin C).

2. Ascorbic acid definitely shortens the paroxysmal stage of the disease, particularly if relatively large doses are used early in the disease.

The ascorbic acid used by us was the Hoffmann-LaRoche product sold under the trade name of "Red-

oxon". Grootton and Bezsonoff⁴ have shown that this product is identical chemically, physically and biologically with the original product prepared by Szent-Gyorgi.

REFERENCES

1. MADSEN, T.: Vaccination against whooping cough, *J. Am. M. Ass.*, 1933, 101: 187.
2. TICE, F.: *Internat. Med. Digest*, 1936, 29: 121.
3. BROWN, H. H.: Whooping cough, *Clin. J.*, 1936, 65: 246.
4. GROOTTON, O. AND BEZSONOFF, N.: Action de la vitamine C sur la toxine diphtérique, et sensibilité du bacille de la coqueluche vis-à-vis de l'hydroquinol et de la vitamine C, *Ann. de l'Inst. Pasteur*, 1936, 56: 413.
5. WORINGER, P. AND SALA, T.: *Rev. franç. de Péd.*, 1928, 4: 809. (Quoted by Grootton and Bezsonoff).
6. GANDER, J. AND NIEDERBERGER, W.: Vitamin C in der Pneumonie-Behandlung, *Münch. med. Wchschr.*, 1936, 83: 2074.
7. HOCHWALD, A.: Beobachtungen über Ascorbinsäurewirkung bei der kruppösen Pneumonie, *Wien. Arch. f. inn. Med.*, (in press). (Quoted by Gander and Niederberger).
8. EVERSON, G. J. AND DANIELS, A. L.: Vitamin C studies with children of pre-school age, *J. Nutr.*, 1936, 12: 15.
9. BESSEY, O. A. AND KING, C. G.: The distribution of vitamin C in plant and animal tissues and its determination, *J. Biol. Chem.*, 1933, 103: 687.
10. YAVORSKY, M., ALMADEN, P. AND KING, C. G.: Vitamin content of human tissues, *J. Biol. Chem.*, 1934, 106: 525.

CHANGES IN CONDITIONED RESPONSES BROUGHT ABOUT BY ANÆSTHETICS AND SEDATIVES*

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PAVLOV⁷ (1927) and his co-workers first observed that conditioned salivary reflexes could be modified by drugs like alcohol, caffeine, chloral hydrate and bromide. Recently Wolff and Gantt⁸ (1935) studied the effects of amytal upon conditioned salivary secretion. The object of the present research was to extend the work to conditioned alimentary-motor responses of dogs and cats. From this viewpoint we have re-investigated the influence of alcohol and of amytal, and tested several new drugs, namely nembutal, avertin, paraldehyde, bulbocapnine, carbon dioxide, ethylene, nitrous oxide, morphia, and hyoscine.

Two dogs and two cats served as subjects. The dogs received sodium amytal and nembutal intravenously, avertin per rectum, alcohol and paraldehyde by stomach tube, and morphia, hyoscine and bulbocapnine subcutaneously. The gaseous anæsthetics were administered to the cats under a bell jar. We naturally waited for full recovery from one drug before we administered a new drug or even a different dose of the same drug.

The general procedure for establishing conditioned reflexes is by now well known. The measured and recorded response may be salivary secretion or any other easily observed reaction (*cf.* Liddell, 1934).

In our work a lid-lifting response was used. This particular training procedure was described by Dworkin² (1935). The stimuli selected comprised auditory, visual and tactile signals. The successive tests were made at intervals of 2 to 6 minutes. During these intervals the animals had been trained not to touch the lid of the food container. Consistent absence of response between stimuli, eventually developed by training, may be called "interval inhibition" (Fig. 1A). The animals were also trained to make two discriminations, (1) between two different buzzers—"coarse" discrimination, (2) between a loud and a quiet musical tone of fixed frequency—"fine" discrimination. The time of incidence of the signals, as well as that of the animals' response, was recorded graphically. Thus we had information as to the latent period, presence or absence of conditioned response, duration of conditioned and unconditioned phases, and finally the amount of interval inhibition.

The latent period of the positive responses varied between 1 and 3 seconds. Often it was just as short for a visual as for a tactile or auditory stimulus. Nevertheless, a loud sound usually evoked a response sooner than a quiet sound; similarly, the latent period for a strong light was often shorter than for a weak light. When a negative stimulus was turned on for differentiation there was at times a slight turning of the head away from the food container, and other signs of general irritation, but no attempt to raise the lid (see Fig. 1B).

RESULTS

Our observations indicate that the eleven drugs tested may be classed into three main

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groups. In one group we should include sodium amytal, alcohol, paraldehyde, nembutal and avertin; in the second group we should place bulbo-capnine, carbon dioxide, nitrous oxide and ethylene; in the third we should include morphia and hyoscine.

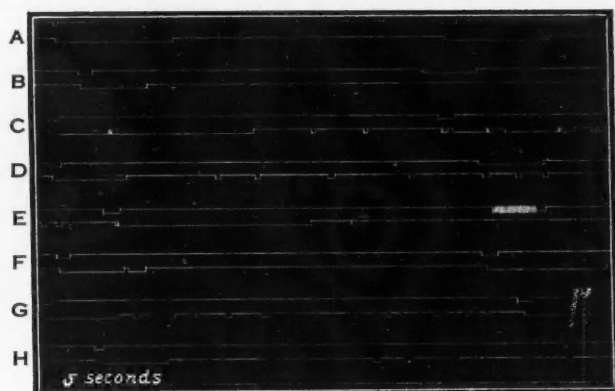


Fig. 1.—A and B: Two records of responses of a normal dog. Read from left to right. The upper line represents the occurrence of the stimuli; the lower line, the opening and closing of the lid by the animal. The distance between any two vertical lines represents 5 seconds. A shows responses to two positive (reinforced) stimuli. The latent periods are very short. In the intervals between stimuli the dog makes no attempt to lift the lid (interval inhibition).

B shows responses to one positive and one negative (non-reinforced) stimulus. The positive stimulus was a bell, the negative a buzzer. Complete differentiation is shown by the absence of response to the negative stimulus sounded for 20 seconds.

C, D and E: Responses to sodium amytal intravenously. In C, the animal received 15 mg. per kg. The responses to two positive stimuli are still brisk, but interval inhibition is replaced by continual activity. In D, the animal received 20 mg. per kg. The responses to the positive stimuli are still brisk; interval activity is persistent, while a negative stimulus now elicits several responses, showing a breakdown of differentiation.

In E, the animal received 30 mg. per kg. Interval activity is still present, but the first positive stimulus elicits a delayed response, while the second is now ineffective.

F, G and H: Responses of dogs that had received alcohol and avertin. In F, the dog received 1.9 c.c. alcohol per kg. (by stomach tube). There is practically no disturbance. In G the dog received 2.5 c.c. alcohol per kg. Interval activity is marked and persistent, while the positive responses are still unaffected. In H, the dog received 110 mg. per kg. (per rectum). Interval inhibition is abolished, while the response to the positive stimulus is still prompt.

1. *Amytal, alcohol, nembutal, paraldehyde, avertin.*—As typical of drugs of the first group a brief account of the action of sodium amytal is given. This anæsthetic was injected at different times, in doses varying from 5 to 35 mg. per kilogram. When 5 to 7 mg. were injected the conditioned responses remained unaffected. At this stage, however, there was a small degree of ataxia or asynergia, specially noticeable during sudden turns, or stops and starts. Further, while ordinary progression was not much affected, the animals were seen to have lost their usual sureness when jumping on or off the observation platform. After 10 to 15 mg. per kilogram had been injected, the

ataxia was more pronounced. The responses to positive stimuli were in no way diminished, but the negative stimuli lost their usual effects. Interval inhibition, hitherto a striking feature of the animal's behaviour, was suddenly replaced by frequent openings of the lid (*cf.* Fig. 1C). At about this time, too, differentiation was much impaired. Often the animal raised the lid promptly when a (hitherto) negative stimulus was presented (*cf.* Fig. 1D). At other times a negative stimulus evoked a delayed response, showing some vestige of inhibition. As a rule we found that the dosage-threshold for the abolition of "fine" discrimination was the same as for abolition of "coarse" discrimination.

Twenty-five to 30 mg. per kilogram was the smallest dose that interfered with the positive responses. The ataxia was marked, while interval activity was persistent. Some responses were completely abolished, others occurred only after a long latent period (*cf.* Fig. 1E). There was no consistent order of disappearance of responses to the different stimuli, although a loud sound usually evoked a delayed response after a tactile or visual stimulus had proved ineffective. The last item of the animals' reaction to disappear was eating of the food (the "unconditioned" response). This occurred when about 35 mg. was injected. Even then the dogs still showed their interest in the food by moving their heads toward the food container.

To summarize, during the action of sodium amytal we were able to observe five well marked pre-anæsthetic stages. These successive stages were: (1) ataxia or asynergia; (2) loss of interval inhibition; (3) loss of differentiation; (4) loss of the positive responses; (5) loss of the unconditioned responses.

Alcohol, nembutal, paraldehyde and avertin had very similar effects. Naturally, the amount necessary to produce any particular stage varied with each drug. In the case of avertin, 35 mg. per kilogram (rectal injection) induced ataxia, while 45 mg. induced loss of interval inhibition and of differentiation (see Fig. 1H). Positive responses did not begin to disappear until 140 mg. had been administered. Of nembutal, 5 mg. per kilogram caused ataxia, and 10 mg., loss of the interval inhibition and weakening of differentiation. With regard to

alcohol, the figures varied considerably, owing perhaps to differences in rate of absorption, or possibly to tolerance. Usually 2.5 c.c. of pure ethyl alcohol per kilogram induced ataxia and loss of interval inhibition (see Fig. 1F and G), but not always loss of differentiation. The latter occurred with 3 to 3.5 c.c. About 5 c.c. were required to abolish positive responses.

In the case of the drugs in this first group, recovery from single doses occurred in from 12 to 36 hours, depending upon the amount injected. At the end of the stated time all positive and negative responses, as well as interval inhibition, had resumed their original strength.

2. *Bulbocapnine, carbon dioxide, nitrous oxide, ethylene.*—Bulbocapnine was administered at different times to the dogs in doses of 0.5, 1 and 5 mg. per kilogram subcutaneously. It caused more or less complete suppression of all conditioned responses, whether positive or negative, and much depression of the unconditioned response. In spite of this, the dogs remained alert, and, to all appearance, unduly apprehensive. While they ignored the positive stimuli, and even refused to obtain food for themselves when the turn-table which carried the food-dishes was operated from the control room, they often accepted the same food when it was offered by hand. The depression was not, therefore, due to derangement of appetite. From the depressant action of bulbocapnine, spontaneous recovery occurred in two to seven days. Nevertheless an immediate removal of the inhibition could be induced by injection of a small amount of sodium amytal.

Carbon dioxide, nitrous oxide and ethylene were administered to cats under a bell jar. The amount varied in different experiments, as did also the percentage of oxygen mixed with the anæsthetic gases. The predominating effect, regardless of the amount inhaled, was depression. Interval activity, while occasionally observed, was not a striking item of the animals' behaviour. The positive responses were either much delayed or completely abolished. The duration of the depression depended upon the amount of oxygen taken with the anæsthetic. When the proportion of oxygen was 15 per cent the responses returned to normal in 5 to 20 minutes after administration had ceased. When the anæsthetics were not mixed with oxygen, the reflexes were depressed as long as 24 hours.

At the end of 30 minutes or one hour the cats might accept food that was handed to them, but showed no recognition of the conditioning signals. This prolonged depression must be attributed to the anoxæmia during the time of administration.

3. *Morphia, hyoscine.*—Both drugs had a powerful effect in doses that were too small to induce ataxia. As an example, 1/60 grain (1.08 mg.) of morphia per kilogram, or 1/75 grain (0.87 mg.) of hyoscine repeatedly abolished some or all of the conditioned responses. This inhibitory action we are inclined to attribute not to a primary effect upon excitatory or inhibitory processes but to nausea and disturbance of appetite. Inhibition of this sort is, obviously, a different thing from that produced by the other drugs.

COMMENT

The outstanding effect of the drugs of our first group was a decided weakening of the negative aspects of behaviour. The result was reappearance of activity suppressed long ago in the course of training. Nikiforovsky,⁶ (1910) in Pavlov's laboratory, was the first to show that small amounts of alcohol abolished discrimination between stimuli and restored an extinguished positive reflex. These effects were attributed by Pavlov to a weakening or abolition of the processes of inhibition, and therefore called "disinhibition". The disinhibiting action of alcohol was confirmed by Andreyev¹ (1934) and in part by Gantt³ (1935). Among other drugs tested in Pavlov's laboratory caffeine also produced disinhibition. Our findings obtained with the alimentary-motor method are in full agreement with those of the Russian workers in respect of alcohol, and reveal four new drugs which can cause disinhibition. Probably this property of "disinhibiting" belongs to many other commonly used sedatives, narcotics, etc. To this action one can attribute the beneficial effects of a drug like sodium amytal in psychotic human subjects (*cf.* Lindemann and Malamud,⁵ 1934). It is significant that the most striking changes have been produced in depressed, "negativistic" patients.

The chief effect of the drugs in our second group was suppression of the usual activity. The first explanation that presents itself is that the processes of excitation primarily were de-

pressed. Against this is the observation that the dogs that received bulbo-capnine were, if anything, even more alert than ordinarily. Then, too, amytal was able promptly to remove the depression. A logical inference is that bulbo-capnine works by spreading and deepening inhibition. Pavlov (*l.c.*, p. 278) quotes experiments by Lebedinsky with chloral hydrate and urethane. Emphasis is placed on the uniform depressant action which resulted in weakening of all positive salivary reflexes.

SUMMARY

Eleven drugs were administered to conditioned animals and their effects upon alimentary-motor responses studied. Alcohol, amytal, nembutal, avertin and paraldehyde were effective primarily in weakening the processes of inhibition. Bulbo-capnine, carbon dioxide, nitrous oxide and

ethylene had a uniform depressant action. Morphia and hyoscine abolished the positive responses, seemingly by producing nausea and loss of interest in the food.

REFERENCES

1. ANDREYEV, L. A.: The effect of single and repeated doses of alcohol on conditioned reflexes in the dog, *Arch. Internat. de Pharmacodyn. et de Therapie*, 1934, 48: 117.
2. DWORKIN, S.: Alimentary motor conditioning and pitch discrimination in dogs, *Am. J. Physiol.*, 1935, 112: 323.
3. GANTT, W. H.: Effect of alcohol on cortical and sub-cortical activity measured by the conditioned reflex method, *Bull. Johns Hopkins Hosp.*, 1935, 56: 61.
4. LIDDELL, H. S.: The comparative physiology of the conditioned motor reflex, *Comparative Psychology Monographs*, 1934, 11: No. 1.
5. LINDEMANN, E. AND MALAMUD, W.: Experimental analysis of the psychopathological effects of intoxicating drugs, *Am. J. Psychiat.*, 1934, 13: 853.
6. NIKIFOROVSKY, R. M.: Pharmacological methods in application to conditioned reflexes, thesis, Petrograd, 1910.
7. PAVLOV, I. P.: Conditioned Reflexes (Translation of G. V. Anrep), Oxford Univ. Press, London, 1927.
8. WOLFF, H. C. AND GANTT, W. H.: Caffeine sodiobenzoate, sodium iso-amylethyl barbiturate, sodium bromide and chloral hydrate: effect on highest integrative functions, *Arch. Neurol. & Psychiat.*, 1935, 33: 1030.

THE PATHOGENESIS AND PREVENTION OF SUICIDE*

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LOUIS I. DUBLIN¹ gives a minimum estimate of 310,000 suicides a year in the world. Canada contributes her share to this astounding number and should take an active part in preventing its growth. It was with this idea in mind that the Toronto study was undertaken, the work covering 352 consecutive cases of attempted suicide admitted to the Toronto Psychiatric Hospital from November 1, 1928, to October 31, 1935.

Statistics for the city of Toronto show that the death-rate from suicide is parallel with such well known diseases as diabetes, influenza and appendicitis. The suicide rate is, of course, minimal, because a certain proportion are unproved and therefore listed with sudden deaths attributable to diseases of the heart and to accidents. In Toronto from 1929 to 1935 inclusive there were 626 deaths from suicide, that is, at the rate of 14.7 per 100,000 population. At the same time 352 cases of attempted suicide were admitted to the Toronto Psychiatric Hospital; 10 of this group died, leaving 342 survivors. There were then, in all 968 known

cases of attempted suicide during a 7-year period in Toronto, with 626 deaths, or a mortality rate of 64.7 per cent for all cases. The mortality rate for females alone was 44 per cent as compared with the exceptionally high rate of 78 per cent for males. Thus, even with scattered, imperfect, and often contradictory evidence, it is obvious that suicide is a problem which should arouse public interest.

SUICIDAL DATA, 1928-1935 (CORRECTED WHEREVER POSSIBLE FOR 100,000 POPULATION)

The highest number of admissions to the Toronto Psychiatric Hospital was for the years 1930 to 1932; for the same period a correspondingly high number of attempts at suicide was registered. In 1933 the general admission number decreased from 846 to 714 and the suicidal admissions decreased from 58 to 46. The admissions for the next two years remained stationary and the suicides dropped to 31 in 1934 and 39 in 1935. If a curve is plotted between the total number of suicidal admissions and the total number of admissions, it will be found that some positive correlation is suggested between the two groups. This may, conceivably, be due to the fact that periods of

* An abstract of a thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy in the University of Toronto, May, 1936.

stress bring out other forms of mental disease as well as suicide. It is further shown that the percentages for females in the attempted suicide group are more constant and at all times higher than for males. A possible explanation for this is that women are not so influenced by world events as men, and that there is a higher instance of fatal suicides in the male group.

In regard to the seasonal incidence of suicide, the end of September sees the beginning of the rise which cumulates in the highest number of suicidal admissions in the month of November. Gradually the curve descends to the low for the year in January. This is followed by a sudden rise in February, which drops to a lower level for the spring months, March, April and May. Another rise occurs in June and is maintained for the summer months July and August.

The birthplace of those attempting suicide in order of increasing rate per annum per 100,000 native-born was recorded. The rates for France 31, Ukraina 42, Switzerland 43, and Belgium 68, are exceptionally high. The suicide rate among the native-born is the lowest, only 6.7; Poland is next, 6.9; England, 8.5; Scotland, 9.6; Ireland is high, 12.8; Wales, 12; and the United States of America is still higher, at 16.5.

The average length of residence in Canada for the foreign-born group was 20 years, the minimum 1 year, the maximum 63 years. It is quite evident that the early years of adjustment to a new country are not the dangerous ones.

The age of those attempting suicide according to sex was noted. The rate for attempted suicide in the male is lowest from 10 to 19 years, gradually rises to between 40 and 49 years, descends irregularly to another low between 70 and 79 years. The curve for the female starts at a much higher level in the age-group 10 to 19 years, and ascends sharply to between 20 and 29 years, gradually dropping to a much higher low than the male in the 60 to 69 year age-group. A likely explanation for the rise in the rate for females between 20 and 29 years and for males between 40 and 49 years is that marriage plays a part in a woman's life that is commensurable with the part played by business in the life of a man. Thus the success or failure of the marriage

attainment is usually between 20 and 29 years; the success or failure of the establishment of man in his trade or profession is between 40 and 49 years.

Practically all classes of occupation were represented. The artisan-mechanics and labourers in the male division, numbering 36 and 33 respectively, and the housewives and domestics in the female division, numbering 88 and 72 respectively, are high, but this class of person occurs in large numbers in the general population. Suicidal acts are not associated with any one type of employment, but rather are dependent on whether the occupation satisfies the individual's requirements mentally, physically and materially.

The total number of attempted suicides was also arranged according to sex and civil status and the rate per annum per 100,000 of the status class. The rate for married men is 9.3, for single men 6.8, and for widowers 11.9. Apparently marriage and the responsibility of the home is a factor in the masculine suicidal rate. The rate for the widower class is high, but this group in the population is small, and also it may be true that widowers find it more difficult to adjust their lives after their partners are removed by death than widows do. The rate for married females is 12.2, for single women is 12.4, and for widows, 7.4—marriage has had no effect.

The various methods used by the patients in their suicidal attempts were listed. Poisoning was favoured by the women and the poisons used were the common ones which are handy in almost all medicine cabinets—lysol, iodine, bichloride of mercury, A.B.S. & C. tablets, etc. Stove gas was used by both men and women, but it is more accessible to the housewife and domestic, and a large percentage of this group used it. The figure for poisoning by car-exhaust gas is very low, which suggests that it is in all probability usually successful, and hence persons using it are not admitted to the Psychiatric Hospital. Jumping from heights, cutting, and shooting are ways preferred by men. The few patients who used burning and mutilation were mentally ill.

The hospital drew its attempted suicide population from the following sources: 151 from general hospitals direct, 125 from their homes, 126 from the police court (71 spent

some time in a general hospital only to find themselves under arrest when ready to be discharged. They were arraigned before a magistrate and then remanded to the Psychiatric Hospital for care). Two patients managed to get home after their sojourn in the general hospital before they were arrested.

With regard to disposal; 197 patients were admitted through the courts but only 154 returned to the courts. Certain persons do not again reach the court. (1) If a warrant patient is found to be mentally ill he is transferred directly to one of the Ontario mental hospitals. (2) In many cases an effort is made to have the patient discharged to his home with the magistrate's approval, in order to prevent further psychic trauma. Of those admitted, other than through the court, 10 died as a result of their self-inflicted injuries; 119 were discharged in good health and wherever possible would continue to enjoy the supervision of the hospital through the out-patient department; 109 were transferred to Ontario mental hospitals because of mental disease, alcoholism or drug addiction.

The following diagnoses of the attempted suicides were made: manic depressive psychosis, depressed phase, 69; reactive depression, 65; neurasthenia with depression, 19; depression with alcoholism, 18; involutional melancholia, 15; etc. The second largest and the most interesting group is the normal, with 67 cases (including dull normal). In fact the majority of those with reactive depression could be transferred from the depressive list to the normal division, as their depression was usually of a temporary nature and reasonably attributable to the overwhelming power of more than a fair share of problems and difficulties. The psychopathic personalities, 19; the mental defectives, 17; and those of hysterical constitution, 16, tend to be numerous and are very refractory to treatment. Their impulsive natures are such that repetition of the act is to be expected. The toxic psychosis group has 10 cases. The possibility of suicide in such patients should be brought to the attention of physicians, as it is a great pity that these people should lose their lives during a temporary period of confusion and delirium when they are in no way responsible. Close vigilance is indicated on the part of everyone in attendance. The remaining cases are divided

into some 20 classes of mental disease which allows from 1 to 6 to a class. It is a miscellaneous group varying for every hospital and not requiring special consideration.

Further information of a more personal nature was secured from patients admitted to the hospital from November 1, 1930, to October 31, 1935. The last two years will receive special mention. During this time 70 attempted suicides were admitted, but 3 were withdrawn from the records due to incompleteness of the data concerning them. Of the 66 patients 2 had previously been in the Psychiatric Hospital because of suicidal attempts; 6 had been in the hospital for periods of observation because of reported psychotic manifestations, but had shown no evidence of suicidal intent; 5 had been diagnosed as suffering from mental disease and had been cared for in Ontario mental hospitals; 1 had been in a mental hospital in England and had had 11 admissions to the Buffalo Psychopathic Hospital. The diagnosis in this last case was psychopathic personality. In all, 15 patients, or 22.3 per cent of those admitted in the two years, had previously been in mental or psychiatric hospitals.

The family history in 21 cases revealed various psychopathic factors and suicidal acts, and 7 of these showed more than one pathological trait. These factors might be considered as influencing the conduct of the patient from the hereditary or environmental standpoint, or both.

The milieu of the cases of suicidal attempt was carefully studied. Living at home were 65.7 per cent. This means that they lived in a family group consisting of parents and siblings, or, if married, with husband or wife, and children. Apparently, the home was not so stabilizing as one would expect. Almost 12 per cent lived alone, and the remaining 22 per cent were about equally divided between relatives, friends and employers: 72 per cent considered their surroundings congenial, and 22 per cent rated them as uncongenial. The latter group did not feel that the disagreeableness of their environment was significant in their form of behaviour. It cannot, however, be ruled out as a contributing item because the majority of this group were not in a position to give an impartial judgment. They had in part become so accustomed to their habitat that they considered themselves immune to its pervading

power, and did not realize it was warping their outlook. Finally, it is noted that 88 per cent of the patients had spent their lives in the city. It must be remembered that the hospital draws its population from Greater Toronto. But, even with this in mind, one would expect to see more people from the country who had perhaps in later life come to reside in the city. It is possible that such a group exists in the outskirts of the city or in Lesser Toronto and would not reach the Toronto Psychiatric Hospital. It so happens that the years 1933 to 1935 were not ones to encourage out-of-town persons to seek city positions, and in this way would limit the number of country-bred persons in the city.

The educational achievement of the patients was studied. Except for illiteracy, comparable figures for the education of the general population are not available. In 1931, 4.3 per cent of Canada's population could neither read or write. This is low compared to the 10.6 per cent in this study; 30 per cent of the group had preparatory school education, 20 per cent had secondary school education and 7.5 per cent continued in normal school or university. Seventy per cent of those starting preparatory school and 80 per cent of those commencing secondary school did not complete their course. These figures must be high compared with the educational achievement of the general population.

The employment data showed that among the men 57.1 per cent were employed and 25 per cent unemployed. The unemployment played a principal part in the suicidal attempt in all but one case. There were 3 not gainful workers; this means younger persons living at home and older retired men; 7.1 per cent were on military or old-age pension. On the female side the ungainful worker group is the largest, due to the presence in it of the housewife. Of the gainful female workers 21.5 per cent were employed and 13.2 per cent not employed. Only two married women tried to work outside the home, and one of these only did so because her husband was unemployed; the second one worked with her husband in a gentleman's club.

Eight of the suicidal housewives had unemployed husbands and the family was on relief or so financially embarrassed that suicide seemed like a simple means of escape. One woman suffered from a reactive depression due to the disgrace of having to receive relief. Six families

receiving small incomes from employment or some other source were still unable to eke out an ordinary existence, and the worry over the financial distress was a contributing item in the act of self-destruction. Twenty persons, or about 30 per cent, manifested asocial habits. One had been convicted of crime, 1 was a prostitute and thief, 1 was a sexual pervert, 3 gave a long history of extra-marital relations. Six of the 14 alcoholics were free from other unpleasant habits, but the remaining 8 were linked up with drug addiction, thieving, untruthfulness, perversion, masturbation to excess, and extra-marital promiscuity.

The relation of interests to suicidal attempts is striking. Twenty-two per cent are reported as having outside interests but they could not be classed as hobbies or as requiring much expenditure of mental effort on the part of the patient. One person was keen about reading and received considerable enjoyment from it; the remaining 12 were limited to movies, bridge and simple concert entertainment. On the other hand, 74 per cent had absolutely no interests apart from their immediate environment.

The data on religion are contrary to those found in other studies. Protestants constituted 61.2 per cent of the attempted suicides, Roman Catholics 29.8 per cent, and Hebrews 7.5 per cent. When these figures are corrected for 100,000 of denomination in the population, the rate is Protestant, 4.5; Roman Catholic, 11.0; Hebrew, 5.6. The findings of this study can be partly explained by (1) that the Roman Catholic population in the city is in the minority, and (2) the number of foreign-born who attempted suicide was high, and a very large percentage of the foreign-born are Roman Catholic. The high Jewish rate is probably dependent on the close correlation between their existence and trade. The recent low ebb in industry would have a proportionately greater effect on their lives. Almost 75 per cent of the patients were listed as having poor religious feeling. This group was really completely indifferent to the subject, and consequently could get no security from their beliefs.

In regard to the marital state as a factor—54.5 per cent of the attempted suicides were happily married. Of the 20 cases of unhappy marriages (45.5 per cent) all but one gave

marital discord as a contributing factor in the final episode. Although conjugal dysharmony is given as a contributing factor in almost half of the cases it is only given as a causal factor in 2. Of the 20 cases of incompatibility mentioned, 4 were due to alcohol, 4 to venereal disease, and 1 to Huntington's chorea.

In the 67 cases in which it was possible to ascertain the health of the individual, 10 men and 14 women were in good health, 8 men and 18 women in fair health, and 7 men and 10 women in poor health. Good health was taken as meaning a well developed, well nourished person with no history of serious illness and no subjective or objective findings of disease. Those in fair health were generally below par, due to past illnesses or a curable pathological lesion. Those in poor health were underweight, undernourished, and suffering from a chronic debilitating condition or an incurable organic disease.

In 6 females disturbance of menstruation and the menopause influenced the act. In 4 of the 10 cases of venereal disease their condition was a contributing factor, and serious illness in 2 where pain and suffering were directly responsible. In all, 26 per cent of the women and 32 per cent of the men cited health as a decisive circumstance.

In analyzing the attempts it was discovered that 41.8 per cent were genuine, 26.9 per cent impulsive, 16.4 per cent spurious, and 4.5 per cent accidental. Only 22.4 per cent gave thought to careful preparation beforehand in order to insure the success of their undertaking. The hours of choice for attempting the act were from 6.00 to 9.30 p.m. and 1.00 to 9.30 a.m.

MOTIVES AND GENERAL REACTIONS

One can only comment on the motives and general reactions concerned in the suicidal attempts. It was found impossible to get a graphic account of the attempt. Among the mentally ill patients this was due to the fact that satisfactory rapport was not obtainable, and in the normal group, to colouring and distortion of actual facts. Some of the motives were: to frighten her husband, to frighten his girl friend, to secure attention (spectacular episode), to avoid failure, to avoid insanity, to avoid the disgrace of poverty, to leave her husband free to return to his mother, to get

rid of feeling of depression, "fed-up", "just felt like it". Several were under the influence of alcohol and denied any motive. No typical remarks were made by the suicidal patients. Those who repeated certain phrases over and over belonged to the manic depressive groups, and the phrases were those usually associated with this form of mental disease.

It would seem that no one considered the legal or religious aspect immediately beforehand, and there was no depth of sense of obligation to others. Apart from the cases of mental disease, the majority were pleased that their attempt had been a failure, and after a short course of psychotherapy developed a good attitude to the future.

SUMMARY

A study is presented of 352 cases of attempted suicide admitted to the Toronto Psychiatric Hospital from November 1, 1928, to October 31, 1935.

The cases received physical and mental examinations and the actual suicidal attempts were studied in relation to basic and immediate causal factors. The results were then corrected whenever possible for numbers of the class in the general population.

SUGGESTION

It is suggested that suicide may be prevented by:—(1) raising the standard of educational achievement of the populace; (2) good mental, physical and public health measures; (3) teaching certain groups among the laity and professions an appreciation of suicide danger signals; (4) abolishing the stigma attached to the act; (5) minimizing publicity; (6) protecting heights by simple, practical means; (7) encouraging medical books to allow more space for information on suicide; (8) elaborating the teaching in regard to suicide in medical, social and legal schools; (9) training youth to take responsibility; (10) encouraging any factors which will build up the solidarity of the group in which the individual finds himself; (11) an investigation to ascertain why there is a greater tendency for foreign-born persons to suicide than native-born; (12) establishing a fixed regular routine day for the unsettled person which will bring satisfaction and contentment to him; (13) establishing clinics to which such distressed persons may come for help and guidance.

REFERENCE

1. DUBLIN, L. I. AND BUNZEL, B.: *To Be or Not To Be*, Harrison Smith and Robert Haas, New York, 1933.

THE EFFECTS OF THEELIN ON ANXIETY

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WE are reporting an investigation into the effects of the ovarian hormone, theelin, upon anxiety. Disorders of the sex life, whether based upon physiological or upon psychological factors, have been frequently associated with anxiety. It has long been conjectured that anxiety associated with the menopausal psychoses in women has its origin in a disturbed function of the glands controlling sex activity. Frustrated sex activity was at one time considered by Freud¹ as a cause of anxiety. His recent writings render his position on this less clear.² The tendency to trace connections between abnormalities of the sex life and anxiety is further supported by the observation that removal of the ovaries is frequently followed by a syndrome in which anxiety is prominent. Werner^{3, 4} has investigated a group of castrated women, and has found that many of the symptoms and signs are those usually associated with the menopause.

It is desirable at this point to clarify our thinking in regard to "anxiety". Until recently anxiety has been primarily considered a "mental" symptom, and study has been directed almost exclusively to its mental manifestations, namely, to the subjective experiences of the patient and to the reports which he is able to furnish. Since the work of Pavlov and his school on the production of neuroses in animals, and more especially since the investigations of Cannon into the body changes in response to emotion, it has become apparent that the whole organism participates in the reaction which we term anxiety. The achievement of this viewpoint is in itself of considerable importance, and leads to two corollaries which are of even more moment.

The first of these is that, since the whole organism throughout its various levels of function is involved, it may be that it is possible to provoke the reaction by stimuli applied not merely at the higher, "mental", levels but at the others as well. This is found to be the case.

In general, it may be said that fruitful causes of anxiety consist in conflict between the desires of the individual and the restraints of the current ethical code. Subjection of the individual to situations which threaten his security is a further situation which in general tends to evoke the anxiety syndrome. This is, of course, well shown in the reactions to war dangers as well as to the present economic uncertainty. But other agents may also produce anxiety symptoms, such, for instance, as sodium cyanide and cocaine under certain circumstances. Anxiety is moreover especially associated with certain diseases, such as Graves' disease, angina pectoris, and other cardiac disorders. The second corollary is that since the whole organism is involved, and since the reaction may be provoked by stimuli at various functional levels, then possibly therapeutic results may be obtained by interference at other levels, even if such therapy were only of the same order as digitalis in auricular fibrillation, *i.e.*, successfully preventing abnormal manifestations. In other words, therapy other than psychotherapy, which is still difficult, poorly understood, and time-consuming, might prove of value. This second corollary constitutes the basis of the thinking underlying much of the medicinal investigation and treatment, not only of anxiety but of mental disorders generally.

The basic manifestations of the anxiety syndrome as provoked by these various agents do not differ substantially from each other. In all of them the vegetative nervous system plays an outstanding rôle. Where, however, the anxiety has been of long duration or has been repeatedly elicited the picture may undergo varying degrees of elaboration. Misch⁵ describes these as attempts on the part of the organism to protect itself from the suffering attendant upon the appearance of anxiety.

It is necessary to point out that the syndrome of anxiety is quite amœba-like in form. Emphasis may in any given case be laid on any

one particular component. It is to be repeated that none the less the whole organism is involved. The manifestations of the vegetative nervous system are especially important. Indeed, in the case of anxiety arising in connection with the menopause these latter symptoms are especially in evidence. Lange⁶ has pointed out that although the objective signs of anxiety may be well marked in these menopausal cases of anxiety the patient herself may make few appropriate and relevant complaints. Apart from anxiety, these patients not infrequently complain of pressure, especially on the head or abdomen. At other times a sense of something impending is felt, or the anxiety may show itself in the form of over-conscientiousness, in difficulty in meeting people, or in anxiety dreams. Objective signs of importance are increase in the pulse rate or the respiratory rate, sweating, pallor or dilatation of the pupils. Gastric disturbances and loss of weight may be associated with long-standing conditions.

Theelin is the ovarian follicular hormone, first isolated in crystalline form by Doisey⁷ in 1930. Its properties and its interrelations with other endocrine substances have been the subject of intensive investigations in recent years. The more firmly established facts regarding its action are as follows. Theelin may be obtained from the follicular liquor of the ovaries. It is also present in large amounts in the urine of pregnant women. This latter fact constitutes the basis of the Aschheim-Zondek test. When injected into adult animals theelin will produce oestrus. Continued injection into immature animals results in the development of maturation and the establishment of oestrus. Clinically it has been used in a wide range of conditions. Allen⁸ had found that the vaginal mucous membrane of the immature monkey developed into an adult type after the administration of theelin. Lewis⁹ applied this finding to children suffering from gonorrhoeal vaginitis, with excellent results. The vaginal mucous membrane assumed the adult type which has long been known to be almost immune to gonorrhoea. Theelin has also been used with benefit in functional amenorrhoea and in oligomenorrhoea. Finally, it has been used to relieve the symptoms arising in castrated women (Werner¹⁰ and Werner and Collier¹¹), and in women at the menopause. The work of Werner and his as-

sociates in this field has been particularly significant. In two recent articles^{12, 13} they claim to have produced marked alleviation and even cure in cases of well developed involutional melancholia. Their theory of the action of theelin in this connection is based primarily on the fact that the symptoms appearing in castrated women and in women at the menopause are essentially similar. They consider that as a result of the interference in the function of the gonads there results an imbalance in the action of the interrelated endocrine glands, such as the thyroid, adrenals, anterior and sometimes the posterior pituitary. This, they claim, in turn affects the balance of the two components of the autonomic nervous system, and the majority of the symptoms are the result of this secondary disturbance. Finally, Werner and his group consider that the anxiety psychoses occurring at the involutionary period are simply exacerbations of these symptoms. The fact that we have found, as shown later, that theelin has no favourable effect upon anxiety not occurring at the menopause further suggests, too, that it acts not directly on the autonomic nervous system but indirectly by restoring an endocrine balance. Heinze¹⁴ in a review of recent progress in the treatment of mental disorder by endocrine substances, reports favourable results obtained by Goldsmith, Dlüber, Holthouse, using various ovarian preparations in disturbances occurring at the menstrual and involutional periods. Holthouse is reported as having obtained good results from the use of ovarian hormones and anterior pituitary in the climacteric psychoses, but no favourable results in senile and arteriosclerotic depression, or in melancholias, apart from the involution or in depressively coloured hypochondriacal conditions.

As can be readily seen from the summaries, the cases can be divided into two groups on the basis of their clinical description and on the basis of their reaction to theelin. The first group consists of those in whom the anxiety syndrome is clearly associated with the menopause. The second group consists of those in which the causes of the anxiety are various. In some a frank conflict between the sex needs of the organism and current ethical standards appears to be the causative factor. In others the genesis is quite unclear, and if we take refuge

in the statement that it appears to arise from conflict we only do so on the basis of the general concept that conflict is a frequent cause of anxiety. The reactions of these two groups to theelin is quite different and it is important to differentiate early between them.

The patient's behaviour was recorded for at least a month on a modification of Kempf's behaviour chart. Theelin was then given intramuscularly in doses of 1,000 international rat-units in oil twice weekly. Progress was checked both by the behaviour chart and by psychiatric interviews.

ANXIETY OCCURRING IN CONNECTION WITH THE MENOPAUSE

In the following cases the anxiety would seem to have arisen at, or been influenced by, the menopause, and it was therefore felt that interference at the physiological level should produce beneficial results. Analyzing briefly the results of treatment in the 11 cases in the series, a satisfactory response was obtained in 6 cases and improvement noted in 4. The last patient in the series, No. 11, has not shown any improvement as yet. It is possible, of course, that she will eventually respond, but since she has already been on theelin six weeks, improvement, if it does occur, should have to be considered as coincidental. It is to be noted that in her case, as well as in Case No. 3, an ovarian operation had been performed. Considering that both these patients showed a less satisfactory response to treatment than others it would seem reasonable to assume that where the issue has been complicated by removal of ovarian tissue the outlook is less favourable. In such cases increased dosage of theelin is probably indicated, this, of course, not being done in our series, since we did not wish to vary the treatment in different cases. We do, however, feel that higher dosages are to be considered as worthy of trial in all cases, and in future it is our intention to use 2,000 units instead of 1,000 bi-weekly.

CASE 1

A 50-year old single woman suffering from chronic neurosis of the obsessional type. She actually does not belong in the present series since she received her theelin treatment about a year before we became interested in our present study. She is included, however, since her symptoms were definitely menopausal in character.

Menopausal changes had been present for six months prior to treatment with theelin. She showed irregular and profuse menses, experienced hot flushes and chilly

sensations, and was subject to attacks of weakness. Mentally she was mildly depressed and irritable and felt tired all the time. She was given six daily injections of theelin 1,000 units in oil, and showed a prompt and satisfactory response to treatment; irritability, depression, and fatigue disappearing. The menses became more regular and flushing and chills were relieved. Since then she has passed through the menopause without disturbance.

CASE 2

A 57-year old married woman with depression at the involutional period. Her illness was of two years' duration, when she became depressed, anxious, and hypochondriacal. Three to four months prior to admission a paranoid trend developed, and she showed ideas of poisoning and became negativistic to food. Menopause was reached at 47. Her family and previous history were essentially negative. Pre-psychotic personality was stable.

Following admission the patient was tense, negativistic, and resistive. Her physical condition was one of severe malnutrition. Tube feedings and intravenous injections were required at the outset. She was started on theelin, 1,000 units in oil twice weekly, and showed a rapid and marked improvement. In three weeks she was going to the occupational class and was discharged as completely recovered. The duration of time on theelin was three weeks.

CASE 3

A 57-year old widow, diagnosed as a manic-depressive (depressed phase). Her illness was precipitated by an operation for the removal of an ovarian cyst eight months prior to admission, her condition being aggravated by the death of her husband three months later. She felt shocked and depressed, complained of flushing sensations about the heart, and loss of strength. She showed a growing lack of confidence and marked indecision. She was admitted to the general hospital for a rest and transferred here a week later, when she became disturbed by the other patients, was panicky, and feared she was going insane. Following admission here she was depressed, tense, mildly agitated and apprehensive, and showed marked indecision. Menopause occurred at 47 and was uneventful. The family history was negative. Her previous history showed nothing of note. She had always been a shy retiring woman with little self-confidence.

She was started on theelin and showed moderate improvement. Her behaviour chart cleared, and her bodily sensations were less marked. Tension was decreased and she felt more confident, though still showing some indecision. She was discharged to the care of relatives, with instructions to continue theelin, but stopped taking it a month later. She then went to Florida for the winter. Reports of subsequent progress indicate that her condition has remained fairly stationary at an improved level. The duration of time on theelin and under observation was nine weeks.

CASE 4

A 61-year old married woman, diagnosed as manic-depressive, (depression). Her illness had begun five years ago with depression and worry over financial affairs. A year later a son committed suicide. She became markedly depressed, agitated, and hopeless. There was some picking and rubbing, and many agitated movements. She felt extremely tense and slept poorly. Self-accusatory ideas were expressed. She was admitted to hospital and was discharged three months later, slightly improved. She remained home only one month before readmission. On her second admission she remained two years. Improvement was only superficial but request for a further trial was acceded to and she was discharged. She again remained on the outside for only a month, when readmission was necessary.

From then until put on theelin her condition remained stationary. Menopause occurred at fifty and was uneventful. Her mother and three daughters had been nervous, and a son had committed suicide. Her previous history was negative except that marital life was perhaps not very satisfactory, although there was no open friction. Personality was fairly open, but she worried easily and was generally rather inadequate.

When started on theelin she was moderately depressed, agitated, and subject to bodily complaints, namely, a "gone" feeling, palpitation, a sense of pressure over the vertex and a tight drawing sensation at the pit of the stomach. She felt generally tense and unable to relax. These feelings, she stated, had never left her since the onset of her illness. Following the starting of theelin treatment she noted improvement in a week's time, and improvement continued until three months later she was markedly improved, bodily sensations being much relieved and at times absent, and she felt much more relaxed. Her behaviour chart compared favourably with the subjective findings. By the end of another two months she was considered as recovered in so far as the anxiety syndrome was concerned, but discharge was delayed owing to the home circumstances, and the fact that as a result of her inadequate personality she had become institutionalized. Gradual pushing was necessary to overcome this, and she was eventually discharged fifty-three weeks after the commencement of theelin treatment. Medication was continued until discharge, but it was not felt necessary that she continue it at home. To date she has made a satisfactory adjustment.

CASE 5

A 66-year old widow. Diagnosis, involutional melancholia. Her present illness was precipitated by financial difficulties and worry over her husband's health. She was depressed, agitated, extremely restless, crying, and continually wringing her hands. Her sleep curve was disturbed. One or two feeble attempts at suicide had been made. Her family history showed an uncle to have had a mental breakdown. Her previous history showed two previous breakdowns similar to the present one, the first following the menopause at 48 years and the second at 53 years. Hospitalization was not necessary with the first attack. She was in hospital one year with the second breakdown. Her interval history showed incomplete recovery on both occasions. Her personality prior to the menopause had been stable.

Theelin was commenced nineteen months following the second admission. Up until this time her improvement had been very slight and her condition had subsided into one of chronic anxious-mindedness with occasional acute exacerbations. She was under constant tension and any attempt to increase her responsibilities was met by a recurrence of symptoms. She showed rapid response to theelin, and improvement was steadily maintained. She herself attributed her improvement to the medication, and a daughter also noticed that improvement was coincident with the starting of theelin, although no explanation had been volunteered to her. Her behaviour chart showed corresponding improvement, and there was a good gain in weight. She was discharged as completely recovered slightly less than a month after treatment was commenced, but was advised to continue treatment at home for a time. She is continuing to do well at home. This case we consider as showing perhaps the most dramatic recovery in any of our series, considering the advanced age and chronicity of her condition along with the completeness and definiteness of her recovery.

CASE 6

A 60-year old widow, diagnosed as a manic-depressive (depression). Her illness began seven months prior to admission following the death of her husband. She became depressed and agitated, felt hopeless, and ex-

pressed suicidal ideas. Later strong feelings of guilt developed. She was eating and sleeping poorly. The family history showed a sister to have had a mental breakdown at the menopause. Her previous history showed her to have been stable until a thyroidectomy at 44, following which she had been nervous and had never completely regained her former health. The menopause occurred at 46. Following admission she was depressed and anxious, hopeless, and marked feelings of guilt were present. She showed no real improvement during her six months in hospital prior to starting theelin.

On theelin, 1,000 units twice weekly, she showed almost immediate response. In two weeks work output increased, she was showing more interest, and her agitation was subsiding. She continued to improve steadily, hopelessness disappeared, and she began to look forward to discharge. Two months later she showed a good gain in weight and was able to enjoy parole privileges. After twenty weeks on theelin she was discharged as completely recovered. She was advised to continue theelin and reduce gradually. She has continued to do well since discharge.

CASE 7

A 44-year old married woman. Diagnosis, psychoneurosis, hysterical type. Physical signs of the menopause, namely, irregular menses, flushing, etc., were present, and it was felt that it was also affecting the mental picture, as headaches, vague anxieties, and some agitation began to show and hypochondriacal tendencies were exaggerated. Her family history was negative. Her previous history showed her to have been neurotic since the age of 16, and her life had been literally a series of operations. Marital life was happy, but coitus interruptus was practised and was considered to be possibly a factor in the production of her anxiety. The husband was also overly sympathetic.

On admission the patient weighed 88 lbs. She showed many post-operative scars, but was physically well, apart from cervical erosion which was treated successfully by cautery.

She was started on theelin, 1,000 units in oil twice weekly. There was no response for a month, then objective evidence was noted, namely, a gain in weight, increased output of work, and improved sleep, sedatives no longer being necessary. For a considerable time she refused to admit improvement herself, although the objective evidence was unmistakable. She continued to improve and was finally discharged after having been on theelin for 17 weeks. At the time of discharge she weighed 105 lbs., was averaging 6 hours sleep nightly without sedatives, in comparison to 3 to 4 hours nightly with sedatives on admission, and was doing a full day's work. She also admitted considerable subjective improvement. The psychoneurotic background was, of course, still present and psychotherapy had been of little avail. Her condition several months after discharge is, however, still improved, and there has been no recurrence of the menopausal symptoms.

CASE 8

A 50-year old married woman. Diagnosis, depression at the involutional period. Her illness had begun four years before with fatigue and inability to do her work. A few months later her father died, and about the same time menopausal changes appeared. Six months later headaches commenced. Vague anxiety and a feeling of tenseness came on, she slept poorly, and had difficulty in concentrating. Her condition remained practically unchanged, except for mild suicidal thoughts prior to admission. Her family history showed the mother and two sisters to be subject to migraine. Her previous history was negative. Personality was stable, except that she had always been a little sensitive and somewhat lacking in initiative. Menopause was completed about three years previously.

Following admission she remained mildly depressed and anxious, though all her symptoms were almost entirely subjective. She complained of dull headache and slept poorly. She was started on the usual theelin routine, but after 25 weeks of treatment shows only slight improvement. Her weight is unchanged. There is some lifting of her depression, suicidal ideas have receded, headaches are improved, and she feels less tense. She is able to concentrate better and there is some return of confidence. Recovery is, however, by no means complete, and her response has been less satisfactory than with other cases of this type. She is still in hospital.

CASE 9

A 47-year old married woman. Diagnosis, depression at the involutional period. Her illness began about three years previously and was gradual in onset. She began to feel inferior in company, mild bodily symptoms appeared, namely, a bad taste in her mouth, nervous swallowing, and a facial mannerism. She grew gradually more nervous, jumpy, and was sleeping only 3 to 4 hours nightly. During the previous year she had had an obsession for cleanliness, gargling her throat frequently, and taking a bath once or twice daily. Signs of the menopause appeared a year ago; flushing, chills, irregular menses, etc. Her family and personal history were negative—a previously stable though rather rigid personality.

She was started on theelin, 1,000 units in oil twice weekly. Her subjective complaints improved, but she continued to sleep poorly. She was a rather uncooperative patient, however, seemingly expecting an almost instantaneous cure, and when this was not forthcoming insisted on her discharge, which was granted. She was on theelin for 19 days while in hospital and showed moderate improvement. Eight months after leaving hospital she returned for advice, and stated that for a month after her return home she did well, then slumped and had been getting steadily worse. Inquiry revealed that she had disregarded instruction as to continuing theelin at home and her slump was coincident with the discontinuance of theelin a month after discharge. She was advised to go on theelin again, but has not reported since.

CASE 10

A 53-year old widow. Diagnosis involutional melancholia. Her illness began six or seven years before, and was coincident with the appearance of the menopause. During the menopausal period she had been a little nervous and emotionally unstable. A year later her sister died of cancer, and the patient became quite run down and slept poorly, and became subject to mild anxiety attacks in the next year or so. She made a partial recovery until her husband died three years before and the home was broken up. She again became depressed and anxious and had great difficulty in sleeping. She was very preoccupied over the necessity of finding a home, and was continually conferring with lawyers and bankers about this matter. Various physical complaints made their appearance, particularly a drawing-tight sensation in the pit of the stomach and a feeling of pressure over the vertex. Tension generally was marked, and she suffered from considerable indecision. Her family and personal history were negative, and she had previously been of a stable personality. Menopause occurred at 46.

Following admission this patient was depressed, generally tense, suffered from marked anxiety and indecision, and showed the bodily sensations previously mentioned. She started on theelin, 1,000 units in oil twice weekly, and showed almost immediate improvement. One week later she was much more cheerful and anxious only at times. She stated that bodily sensations were much improved, and she felt more relaxed. Her sleep curve was much improved, and she was showing a

slight gain in weight. She has continued to do well with occasional slumps, and at the present time shows only occasional anxiety; bodily sensations have disappeared as has also tension. Her behaviour chart is clear, and she is sleeping satisfactorily without sedatives. Discharge has not been effected as yet, but is to be considered in the near future.

CASE 11

Patient is a 53-year old married woman. Diagnosis, manic-depressive psychosis, depressed type with agitation. Her illness began one year before, following the extraction of some teeth, when she began to suffer from lower abdominal pain and worried about her physical condition. Three months later she had her appendix and an ovarian cyst removed. Two days later she became quite depressed, agitated, and panicky, and developed delusions of cancer of the oesophagus. This obsession became so fixed that she could talk of nothing else. She feared food and tube feedings were necessary. She expressed suicidal ideas, but did not act upon them. Her family and personal history were negative. Her previous personality was quite stable. The menopause occurred a little over a year ago and completed nine months ago.

On admission she was extremely agitated and depressed, being firmly convinced that she was suffering from cancer of the oesophagus and she showed a marked fear of food. She was extremely apprehensive, over-talkative, and resistive. Sedatives were necessary to insure sleep. She was started on theelin, 1,000 units in oil twice weekly, but to date has shown no very definite improvement after approximately six weeks of treatment. There have been two periods during which agitation subsided considerably, and it was possible to start her working in the occupational class, but these were both followed by very definite slumps and at the present time she is still extremely agitated and depressed, requiring active sedative treatment.

ANXIETY OCCURRING APART FROM THE
MENOPAUSE

The following group of cases represent anxiety arising in younger women, in whom the anxiety was to be considered as due to several factors, sex conflict being probably the predominant factor in most of the cases. In four of these cases definite increase in symptoms was noted, indicating that stimulation of the sex libido was caused by theelin. In another case (No. 4) some improvement occurred. This was the case of a woman of a rather inadequate personality adopting an hysterical type of reaction to escape her marital responsibilities. In her case it was felt that increasing the sex urge had possibly increased her incentive to face her responsibilities by making the marital state more desirable to her. One case in the series, though definitely presenting anxiety symptoms, showed no response one way or the other to treatment.

CASE 1

A 35-year old married woman who was seen as an outpatient nine months ago. She presented a typical picture of anxiety neurosis, her chief symptoms being restlessness, anxious-mindedness, palpitation, attacks of shaking, occasional numbness of the hands, loss of appetite, and sleeplessness. She was a rather highly

sexed woman, and her condition was apparently due to the fact that she had separated from her husband and was now unable to find any satisfactory outlet for her sex desires. Intercourse had been carried on with other men, but only temporary relief was obtained, and this was followed by increased guilt feelings and anxiety.

Theelin treatment was purely along experimental lines. She was put on 1,000 units in oil twice weekly, but this was continued for only three doses when it was found that the anxiety symptoms were definitely exaggerated, indicating that her symptoms were arising primarily at the level of mentation rather than at the physiological level.

CASE 2

A 29-year old single woman, diagnosed as manic-depressive (depression). The onset of her illness was about 6 months before admission. The patient, a nurse, had been under considerable strain for some time prior to this as a result of one of her patients committing suicide, the knowledge that she was developing pulmonary tuberculosis, and a misunderstanding with her fiancé. She became deeply depressed, retarded, and suffered from strong guilt feelings. She felt that she had ruined her life and begged to be killed. Following admission she showed the typical picture of an agitated depression. The family history showed the mother to be serious minded and inclined to worry easily. Her personal history showed her to have had an illegitimate child at nineteen by an uncle. She had always been quiet, reserved, and inclined to take life seriously, and was subject to periods of mild depression. A physical examination showed minimal inactive tuberculosis and a cervical erosion which responded satisfactorily to the electric cauterization.

The patient was started on theelin, 1,000 units in oil twice weekly, but did not do well. Depressive shading on her behaviour chart increased, and she was also charted as being irritable and resistive. Her menses were not altered. Theelin was discontinued thirteen weeks later. Following this depressive symptoms lifted rapidly, and three weeks later her chart was practically clear. Then her reaction altered and the picture has gradually become schizoid. She is still in hospital and is now showing evidence of deterioration. It is felt that theelin, although increasing sex feelings, acted in a negative rather than a positive way.

CASE 3

A 19-year old single girl. Diagnosis, schizophrenia, catatonic type. Her illness began approximately three years before with a growing lack of interest and character change. A few months later she became depressed and refused to eat, and was admitted to hospital. Following admission she remained depressed, with occasional suicidal attempts. She showed many agitated movements of the hands, with some picking. She made a fairly good recovery, except that her personality remained very rigid and unbending, and she was somewhat remote. She was discharged on trial, after having been in hospital six months, and did fairly well for about a year, when she again became disinterested, quarrelsome and difficult. Irritability was markedly increased at the menstrual period. Suicidal attempts were made. Following re-admission she was excited, over-talkative, showed many mannerisms, was resistive and impulsive, and her speech was incoherent. Her family background is extremely poor, showing five relatives mentally unstable. She was stubborn as a child, but otherwise normal until puberty, when she became increasingly seclusive and withdrawn.

Again treatment was purely experimental in nature. She was started on 1,000 units in oil twice weekly, treatment being continued for six weeks. While on treatment impulsiveness and over-activity increased, and she was definitely more irritable. Suicidal attempts were also more frequent. Following withdrawal she returned

to her former level. The increase in symptoms was again considered as indicative of stimulation of the sex libido by theelin.

CASE 4

A 36-year old married woman. Diagnosis, psychoneurosis, hysterical type. Symptoms commenced about eight years ago following pregnancy. The course was fluctuating in character, the main features being a state of chronic anxious-mindedness, continual worrying over trifles, obsessional ideas and thoughts, hypochondriacal complaints, such as dizziness, photophobia, and peculiar feelings in the head. She was generally depressed and apprehensive, and feelings of impendingness were present. She was subject to acute exacerbations of anxiety, during which feelings of unreality were present. She suffered from palpitations. The family history is negative. Her personal history showed her to have led a rather sheltered life, and from childhood she showed evidence of an inadequate personality with little drive or initiative. At 19 she made a half-hearted attempt at teaching school, but gave it up after eighteen months because of inability to control her pupils. Marriage at 26 resulted unsatisfactorily, partially due to her inability to carry the responsibilities of married life. It was felt that her whole illness represented her attempts to escape from the difficulties of reality and particularly marriage.

Following admission there was no essential change. She was started on theelin, and a slight but definite improvement was noted, in that she became less tense and anxious-minded, and the depressive symptoms lightened, as evidenced by the way her chart cleared considerably. She showed a gain of 10 lbs. in weight and seemed a little more willing to assume her responsibilities as a wife again. It was felt in this case that the increasing of the sexual libido had possibly resulted in giving her a little more drive and incentive to face her responsibilities, with a resulting decrease in symptoms which might be considered as having been purposive in nature. She was on theelin for nine weeks, being discharged to the care of her husband at that time. Since her discharge she has continued to carry on at an improved level.

CASE 5

A 24-year old woman. Diagnosis, schizophrenia, paranoid type. Her illness began about five years ago with depression, suicidal ideas, and auditory and visual hallucinations of a rather mystical religious character and strong sex-colouring. She made a determined suicidal attempt prior to admission. Following admission the patient passed through a period of agitated depression, showing considerable anxiety, restlessness, wringing of her hands, and some picking and rubbing. Following this she made a fairly good adjustment to hospital life but remained mildly anxious and showed marked indecision. Her family history was negative. Her personal history was negative until the age of 18 when she was married at the insistence of her father, the patient not being in favour of the marriage, and this undoubtedly was a factor in the production of her illness. Her personality was seclusive and reserved. She stated that life never had much meaning for her. She was always sexually frigid and had no desire for marriage.

She was started on theelin, on the usual routine dosage. This was during her third year following admission to hospital. Theelin was continued for nine weeks. During this period there was no change either objectively or subjectively.

CASE 6

A 19-year old single girl. Diagnosis, manic-depressive depression. Her illness began about a month before admission, when she became depressed and threatened to shoot herself. Apparently this was

precipitated by a disappointment in love. Following admission she was deeply depressed, markedly retarded, and mute. Her family history showed both parents to be unstable and two sisters are nervous. Her early development was normal. She became very obese at puberty, but regained her normal weight through dieting. She was not considered seclusive, taking a normal interest in community activities. There were no particular sex interests.

She was started on theelin, 1,000 units in oil twice weekly, this being continued for six weeks, during which period she showed no change except for a slight but definite increase in irritability and negativism. Her weight dropped 10 lbs. The menses were not affected. Following discontinuance she showed improvement. Her depression began to lift, and one month later she was much improved. She began to show an interest in her surroundings and talked fairly freely. Following this she showed a definite swing to the manic side and at the present time is definitely hypo-manic. In this case it would again seem that theelin can be considered as having shown some influence on the sex functions, as shown by the slight increase of symptoms during treatment. There is also the possibility to be considered that it initiated her change in reaction.

DISCUSSION

From the results of this investigation it may be seen that where anxiety symptoms seem to arise from the abnormal action of the endocrine glands governing sex activity the use of theelin appears to be almost specific. Where, however, the anxiety arises apparently from other causes, particularly sex conflicts, the hormone is usually contraindicated. Theoretically, it is conceivable that reinforcing of the sex needs might force the organism to make an adjustment or compromise in ethical standards and ultimately reach a more satisfactory working basis. In Case 4, of the second group this would indeed seem to have been the case, but, though in occasional instances, such as that mentioned, the theory might be borne out in actual practice, in the majority of cases it would seem that reinforcing the sex needs alone is inadequate, and indeed may cause less satisfactory reactions to appear. This would seem to have been the result in Cases 1, 2, 5, and 6, of the second group. Consequently, one must proceed cautiously, not only in cases where sex conflict is a manifest causative agent in the production of anxiety but also in those cases where there are possible

latent sex conflicts. Perhaps an attack at the physiological level by means of ovarian hormones combined with psychotherapeutic measures might give more favourable results, but certainly the physiological mode of approach with ignoring of the mental conflicts would seem a risky procedure in such cases. Where, however, the anxiety appears at the menopausal period, where the somatic symptoms of anxiety appear early and occupy a considerable part of the picture, the use of theelin would seem to be of very great value.

SUMMARY

The effects of theelin on anxiety were investigated. It was found that where anxiety occurred in connection with the menopause the results were almost uniformly good. Where it arose apart from this the effects were doubtful, and might even be undesirable.

In conclusion we wish to express our appreciation to Parke, Davis & Co. for their very generous donation of theelin. We are also indebted to Dr. T. A. Pincock for the use of the clinical facilities of this hospital.

REFERENCES

1. FREUD, S.: Criticisms of the anxiety neurosis. Collected papers, International Psychoanalytic Press, London, 1924, Vol. 1, pp. 107.
2. FREUD, S.: Inhibitions, symptoms and anxiety, *Psychoanal. Quart.*, 1935, 4: 616.
3. WERNER, A. A.: Symptoms accompanying ovarian hypofunction, *J. Miss. Med. Ass.*, 1931, 23: 363.
4. WERNER, A. A.: Syndrome accompanying difficulty or absence of the ovarian follicular hormone. *Endocrinology*, 1935, 19: 695.
5. MISCH, W.: Syndrome of neurotic anxiety, *J. Ment. Sc.*, 1935, 81: 389.
6. LANGE, J.: Die endogenen und reaktiven Gemütskrankungen und die manisch-depressiven Konstitution, Bumke, J. Springer, Berlin, 1928, Vol. 6.
7. DOISEY, E. H., THAYER, S. AND VILER, C. D.: Preparation of crystalline ovarian hormone from urine of pregnant women, *J. Biol. Chem.*, 1930, 86: 499.
8. ALLEN, E.: Reactions of immature monkeys (*Macacus rhesus*) to injections of ovarian hormone, *J. Morphol.*, 1928, 46: 479.
9. LEWIS, R. M.: Effects of theelin on gonorrhoeal vaginitis in children, *Am. J. Obst. & Gyn.*, 1933, 26: 593.
10. WERNER, A. A.: The effects of theelin injections on the castrated woman, *J. Am. M. Ass.*, 1933, 100: 633.
11. WERNER, A. A. AND COLLIER, W. D.: Production of endometrial growth in castrated women, *J. Am. M. Ass.*, 1933, 101: 1406.
12. WERNER, A. A., JOHNS, J. A., HOCTOR, E. F., AULT, C. C., KOHLER, L. H. AND WEISS, M. W.: Involutional melancholia, *J. Am. M. Ass.*, 1934, 103: 13.
13. WERNER, A. A., KOHLER, L. H., AULT, C. C. AND HOCTOR, E. F.: Involutional melancholia, *Arch. Neurol. & Psychiat.*, 1936, 35: 1076.
14. HEINZE, E.: Endocrine Störungen, *Fortschr. der Neurol. u. Psychiat.*, 1936, 7: 285.

HONEY FOR PRURITUS VULVÆ.—According to F. Schultze-Rhonhoff there is a large group of cases of pruritus vulvæ which are of obscure causation and in which the most varied lines of treatment prove useless or only transiently successful. In general, irradiation by x-rays and the administration in quick succession of massive doses of ovarian hormone are the most helpful

lines of treatment. Schultze-Rhonhoff and his pupils, however, have recently had excellent results in refractory cases from local applications of honey every evening. The treatment is empirical, for little evidence is forthcoming that honey contains significant amounts of vitamins or hormones.—*Zbl. Gynäk.*, March 13, 1937, p. 610. Abs. in *Brit. M. J.*

THE BIOLOGICAL TEST FOR PREGNANCY

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IN 1930 an investigation was begun in this department to determine the accuracy and usefulness of the Aschheim-Zondek test as an aid in the diagnosis of pregnancy. Dr. G. H. Ettinger was carrying on a similar study in Queen's University at the same time. A joint report from the two laboratories, giving the results on 112 cases in which, following the original Aschheim-Zondek technique mice were used as the test animals, was published in this *Journal*.¹ In 1929 Friedman² described a modification of the test in which rabbits were used. This modification decreased the time required for the performance of a test from 5 days to 30 hours. The shorter interval offered distinct advantages, and, after the accuracy of the Friedman method was confirmed, rabbits were used exclusively in this laboratory. A report in 1933 in this *Journal* summarized the results of approximately 1,600 tests.³

Since 1931 a pregnancy-testing service, conducted with the cooperation of the Department of Obstetrics and Gynecology, has been available in this department. The test has been available to physicians throughout Ontario and has been utilized by physicians within a radius of three hundred miles. Since funds were not available for such routine work it was necessary to charge for the service. Tests have been performed only at the request of a physician, and the result has always been transmitted directly to the physician. A continuous increase in the number of specimens sent to the laboratory presumably indicates that the tests are useful. It has been decided, however, that this type of routine testing is not within the scope of the work in this department. The Department of Pathology and Bacteriology has consented to assume this responsibility, and the pregnancy test was transferred to that department on February 22nd, where it is in charge of Dr. Holman and Dr. Greey. Prior to this transfer 6,522 tests had been carried out. In the report published in 1933 data were given for 1,536 tests; the present communication deals with the results of the re-

mainder (4,986) for which clinical information is available.

The technique which has been employed for the past four years is the same as described in the 1933 report and need not be repeated here. Certain precautions should be emphasized. The rabbits used for this test should be segregated in separate cages and male rabbits should not be kept in the same room. Two injections, twelve hours apart, are much to be preferred to a single administration of urine. The accuracy secured in this laboratory has amply justified the use of two rabbits for each test.

In sending the result of a test to a physician a form letter was used. This contained a questionnaire regarding subsequent clinical findings. Only by the return of these forms has it been possible to gauge the accuracy of the test. In 2,359 tests, 47.3 per cent of the total done in the past four years, the clinicians have co-operated by returning this form, and our thanks are due to them for their assistance. The following table summarizes the results.

Total number of tests here reported.....			4,986
Tests for which clinical information is available.....			2,359
<i>Laboratory test positive</i>			1,079
Clinical diagnosis	{ pregnant	{ normal	1,059
		{ incomplete abortion	5
		{ missed abortion	1
	{ not pregnant	{ hydatidiform mole	2
		{ actual errors in laboratory test	12
<i>Laboratory test negative</i>			1,280
Clinical diagnosis	{ not pregnant	1,207
		{ ectopic	11
	{ pregnant	{ dead ovum	39
		{ actual errors in laboratory test	23

It should be noted that a positive test is not indicative of a living fetus but is due to the presence of active placental tissue. Consequently a positive result should be found in cases of incomplete abortion, hydatidiform mole, ectopic pregnancy and chorion-epithelioma. Strictly speaking, all positive results, other than for cases of pregnancy, should be considered as

errors. On this basis the number of errors when the laboratory test was positive is 20, or 1.8 per cent. Subtracting those tests when a positive result correctly showed placental tissue, the net number of errors was 12 (1.1 per cent of the total). In the second group those cases in which a negative result was secured but in which an ectopic pregnancy was later found are errors in testing, while the 39 cases of dead ovum could not have been expected to give a positive response and should not be classed as incorrect. The total number of errors among the negative tests was 34, or 2.7 per cent. In a total of 2,359 tests incorrect results were secured in 46 (1.9 per cent). Accuracy of this order is probably not possible in any other biological test.

These results show that more negative than positive results were incorrect. At least two factors may be responsible for this. Possibly specimens were secured too early in pregnancy to contain a measurable amount of the gona-

dotropic hormone. Unfortunately information is not available, except in a few cases, as to whether specimens were taken after a menstrual period had been missed. There is little use in doing the test before that time. A second factor may be that some specimens were taken late in the day and were not sufficiently concentrated to give a positive test. Whatever the cause, there is a basis for being more skeptical about a negative than about a positive one.

We are indebted to Dr. J. G. FitzGerald for permission to establish a pregnancy test laboratory in the School of Hygiene, to the many clinicians who have co-operated with us, and to Mr. A. J. McEwen for valuable technical assistance.

REFERENCES

1. ETTINGER, G. H., SMITH, G. L. M. AND MCHENRY, E. W.: The diagnosis of pregnancy with the Aschheim-Zondek test, *Canad. M. Ass. J.*, 1931, 24: 491.
2. FRIEDMAN, M. H.: Mechanism of ovulation in the rabbit. II. Ovulation produced by the injection of urine of pregnant women, *Am. J. Physiol.*, 1929, 90: 617.
3. BEST, C. H. AND MCHENRY, E. W.: The Friedman modification of the Aschheim-Zondek test for the diagnosis of pregnancy, *Canad. M. Ass. J.*, 1933, 28: 599.

THE INDICATIONS FOR BILATERAL ARTIFICIAL PNEUMOTHORAX

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THE treatment of pulmonary tuberculosis has been primarily bed rest since the time of Galen. This remains the approved method of treatment in minimal cases where there is an early tendency for healing and where the family and racial characteristics are favourable. Very far advanced bilateral lung involvement offers no alternative. The use of artificial pneumothorax, phrenicectomy and thoracoplasty in the present century has startlingly improved the prognosis of pulmonary tuberculosis where the involvement, however extensive, has been unilateral. More recently, improved equipment has resulted in intrapleural pneumolysis taking its place as an indispensable addition to the modern treatment of the disease.

Bilateral tuberculosis presents a more difficult problem. Bed rest alone is usually inadequate. Unilateral pneumothorax with bed rest at times proves satisfactory, the contralaterally lesser diseased lung improving with this regimen. Unfortunately the contralateral lung is just as apt to retrogress, and definitely more apt where

cavitation is present. Bilateral pneumothorax has now been proved beyond doubt to be the treatment of choice in these bilaterally diseased cases. Both lungs are collapsed within a short time of each other and the collapse maintained as indicated, possibly for a period of years. These cases are here designated as belonging to Group I. Bilateral pneumothorax likewise supplies the answer to the problem of a new focus or an extension of disease in the contralateral lung where unilateral pneumothorax is already present (Group II).

In considering Group I cases one must first determine the limitations for bilateral pneumothorax. There is no exact yardstick to follow, but as a general rule it may be considered that an involvement of more than half the total area of the combined lungs is a contraindication. In addition, the distribution of disease should be concentrated rather than scattered throughout the entire extent of the lungs. The most suitable cases are those where the disease is confined to the upper third of each side. Long-standing

cases of tuberculosis where the disease is quiescent are frequently better left alone, or, if the indication is present, collapsed only on the more involved side. Thick-walled cavities on both sides do not contraindicate bilateral pneumothorax but the prognosis is less apt to be favourable. The pressure required to collapse these cavities may at the same time over-collapse the remainder of the lungs, with consequent dyspnoea or cardiac embarrassment.

The indications for bilateral pneumothorax are determined largely by means of the x-ray. Other factors frequently influence the course of procedure, but in actual practice it is found that if the x-ray evidence favours the treatment it should be proceeded with boldly. It is almost always possible to retreat without harmful effect if, after establishment, factors prevail which warrant such a decision. Of these, cardio-respiratory embarrassment is the most likely to be met with, but even this is seldom encountered if the procedure is kept within its limitations. Any age up to forty appears suitable for this bilateral collapse. Our oldest patient, 43 years of age, tolerated the treatment almost as well as the younger ones. A moderately low vital capacity need not be a contraindication, because in some instances a successful termination has been reached when as much as approximately two-thirds of the total combined lung area, as demonstrated by x-ray, has been collapsed. Where concentrated sputum tests are negative and no cavitation is demonstrable the indication for bilateral collapse may not be present. If, however, the blood sedimentation rate, temperature, or pulse suggest an active process no delay is warranted. This applies particularly to young patients and to those with known poor family histories.

Where the tuberculous process is mostly confined to one lung it is sometimes preferable to delay the collapse of the other. But there should be no delay in collapsing the contralateral lung after pneumothorax has been well established in the more involved side if the infiltration is greater than one intercostal space or if a cavity is present. It is preferable, but unnecessary, that the first lung should be effectively collapsed before inducing pneumothorax on the other. A cavity may be incompletely closed for a month or two due to adhesions. At this time pneumolysis may be advisable, but in the meantime

we prefer to collapse the other lung, even if only slightly. It must be pointed out, however, that this opinion does not entirely coincide with the general view. Many experienced phthisists prefer to await an entirely effective collapse on the first side, including pneumolysis if necessary, before induction of pneumothorax on the other. The following is illustrative of Group I cases.

CASE 1

A graduate nurse, aged 30; racial origin English. Productive cough and low grade fever for 10 months previous to admission, September, 1930. Sputum positive. The right lung infiltrated to 4th rib anteriorly with cavity 2 x 2.5 cm. at second rib level. Left lung was infiltrated to the third rib with a cavity 3 cm. in diameter at the level of the second rib. Left pneumothorax was induced, October, 1930, and right pneumothorax two weeks later; selective collapse on both sides. The cavity closed within a month on the right side and within two months on the left. The sputum has been negative since. Pleural effusion on right a year after pneumothorax commenced. Pneumothorax was abandoned on this side six months later because of smallness of space consequent upon adhesive pleuritis. Left pneumothorax was discontinued, October, 1934. Both lungs have remained essentially clear. The patient resumed her occupation two years ago but could have done so earlier if this had been necessary.

It will be noted that the cavity was closed a month earlier in the second lung to be collapsed. We feel that it was wiser to induce pneumothorax on this side before the original collapse was entirely effective. In this particular instance two months were saved. This case is interesting inasmuch as pneumothorax was maintained only for 1½ years on the right, yet the end-result has been excellent.

Group II cases have had unilateral pneumothorax for varying periods of time. Commonly, the contralateral lung is involved to a slight extent, and frequently the course of treatment is terminated with this lung improving to the point of complete healing. But how often is this not the case? Formerly it was the practice when an extension of disease occurred on the uncollapsed side to have the patient observe a strict bed regimen and then to hope that time and nature would arrest the process. It is only necessary to have observed with what comparative comfort patients tolerate bilateral pneumothorax to convert one to the desirability of this therapy at the first suggestion of a contralateral spread of disease. The presence or absence of cavitation should not influence the decision. A negative sputum does not indicate that a period of observation should follow. Unquestionably, if this course of procedure is followed there will

be occasional unnecessary collapses but this is wholly justifiable. In view of the fact that complications are few with pneumothorax when the lesions are small no harm is done if the lung should be unnecessarily collapsed for two or three years. Then, too, the prognosis is much less favourable if cavitation develops during a period of observation. Even though a successful pneumothorax is then established it will have to be maintained for a considerably longer time than would have been the case without cavitation.

CASE 2

A factory employee, aged 19; Finnish. A six months' history of productive cough, hæmoptysis and fever prior to admission. The right lung was infiltrated, the upper half with two cavities (2 and 3 cm. in diameter) in the upper lobe. The left lung showed a few scattered areas of light infiltration between first and third ribs. Sputum positive. Blood sedimentation 23 mm. Right pneumothorax was induced, May, 1935. Collapse was effective within three months. Sputum negative. Left pneumothorax was induced, October, 1936, because of extension of disease to apex and low-grade fever. Previously there had been some clearing of infiltration on this side. Sputum negative. The patient was now ambulatory; no symptoms. Blood sedimentation 10 mm.

CASE 3

A graduate nurse, aged 34; English origin. Sudden onset in December, 1930, with fever, productive cough and pain in the right lower chest. Sputum positive. The right lung showed a pneumonic type of infiltration from the third rib to the base. The left lung was lightly infiltrated in first interspace. Right pneumothorax was induced, December, 1930. Collapse was effective within a month and symptoms were absent. One year later there was rapid extension in left upper lobe with cavitation. Left pneumothorax was induced, December, 1931. The cavity closed in March, 1932. The right lung was allowed to re-expand, March, 1934, and the left, March, 1935. The patient has been working on sanatorium staff for past year and remains very well.

The end result in Case 3 was excellent, but obviously an earlier collapse was indicated. After the right lung was effectively collapsed, the sputum negative, and patient ambulatory she was allowed to go home (70 miles distant), returning every two weeks for refills. Films were taken only every three months. During a three months' interval there was extension from a small area of more or less apparently healed disease to the extent of a moderate-sized cavity. Catarrhal symptoms plus elevated temperature were present for a few weeks previously, which were interpreted as being due to a "cold". Case 2 had negative sputum when bilateral pneumothorax was commenced. There was only slight extension of disease at the left apex. The blood sedimentation rate was essentially un-

altered. But because this patient was not ambulatory when the extension occurred, because her racial origin was unfavourable, and because of her age (20) the indications for bilateral collapse were clearly present. Actually, blood sedimentation and the general condition rapidly became better in a short time than they had been at any time since the onset of the illness.

Where unilateral pneumothorax exists and a new focus of disease develops in a previously uninvolved contralateral lung the indication for bilateral pneumothorax clearly exists. This is true even when the amount of infiltration is less than one intercostal space. Depending on certain factors, however, some delay may be justifiable. For instance, if the patient has returned to work during the course of the unilateral pneumothorax and a new focus of disease develops contralaterally it may be preferred to revert to bed rest alone. If this course is adopted stereoscopic x-ray films should be taken every few weeks and the course of the disease carefully watched. Our own preference is not to wait at all, excepting for exceedingly small lesions, particularly where the existing pneumothorax is not entirely effective. There is less likelihood of the newly diseased contralateral lung improving under such conditions than where the collapse of the first lung is entirely effective. When the new focus has appeared during bed-rest treatment, where the patient's resistance is known to be poor, where the family or racial characteristics are unfavourable, and in the ages between 16 and 25, bilateral pneumothorax is strongly indicated.

CASE 4

A window-dresser, aged 23, Irish-Syrian, was admitted, July, 1934. Severe cough; sputum considerable and positive; temperature, 100° F. Blood sedimentation 26 mm. The right lung clear. The left lung was infiltrated from the first to the third ribs, with a cavity 2 cm. in diameter. Left pneumothorax was induced, July, 1934; right pneumothorax, October, 1936. The patient had been ambulatory but developed a new focus at the level of the second rib on the right. Temperature occasionally 99° F. Effective collapse was obtained and the patient was ambulatory again within a month. She was now able to resume her occupation.

CASE 5

A stenographer, aged 34, of Austrian origin, was admitted May 21, 1936. Her general condition was good. Sputum positive. A cavity, 4 cm. in diameter, was present opposite the central root area on the right. The left lung was fairly clear. Right pneumothorax was induced May 27, 1936. A severe febrile reaction in the days following was due to a bronchogenic spread to the left lung. Three days after the initial pneumo-

thorax the left lung was infiltrated between the 4th and 6th ribs, and twelve days after the entire lower half of the lung was involved. Left pneumothorax was commenced June 13, 1936. The temperature remained elevated for nearly two months but gradually returned to normal. The sputum was negative since September, 1936, at which time the large cavity on the right was closed. The infiltration has gradually cleared on the left but not completely as yet. The collapse on this side is only fair but not suitable for pneumolysis. Blood sedimentation has changed from 26 mm. to 10 mm. during the course of treatment. Her general condition very good; no cough, fever, dyspnea or appreciable loss of weight.

Patient No. 4 developed a new focus contralaterally while ambulatory. Symptoms were absent but the temperature was occasionally 99° F. A good collapse was obtained and within a month the patient was again ambulatory. This method of treatment appears definitely superior to that requiring several months or more in bed. Within three months of collapse of the second lung the patient's condition warranted her doing light work. Case 5 illustrates another indication. Here there was a pneumonic type of disease to deal with. Within

two weeks after unilateral pneumothorax was commenced an apparently clear contralateral lung was infiltrated in approximately its lower half. It may be reasonably concluded that without collapse of this lung there would have been a rapid fatal termination. Our only regret is that we did not commence the bilateral collapse two weeks earlier when the new process was first observed.

Although it is true that both lungs may be collapsed to a surprising extent without undue embarrassment to the patient no attempt should be made to induce bilateral pneumothorax where the disease is very extensive. If there seems to be scant hope of arresting the tuberculous process there is little justification for subjecting a presumably quite ill patient to this treatment. On the other hand, collapse of early bilateral lung lesions without delay is unreservedly advocated. The danger of severe complications is negligible compared with the risk of progression of the disease to an advanced and hopeless state.

REPORTS OF CASES OF SEVERE STREPTOCOCCUS HÆMOLYTICUS INFECTION TREATED WITH PRONTOSIL

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IN view of the great interest taken at the present time in the treatment of *S. hæmolyticus* infections with prontosil, reports of three such cases occurring recently in my own practice may be of some general interest.

CASE 1

A female, aged 41, was admitted to the Montreal General Hospital on January 5, 1937. There was a history of a foul discharge from the left ear since childhood, dizziness at times, and deafness in the left ear. On January 6th a radical mastoidectomy on the left side was done and a cholesteatoma found. A small portion of the dura was exposed during the operation.

The patient made an uneventful recovery from the operation, was up and about the ward, but there was still a slight purulent discharge from the middle ear. On January 23rd, 17 days after operation, there was a sudden rise of temperature to 102° F.; the patient felt dizzy and a slight nystagmus to the left was noted. There was a moderate exaggeration of the knee jerks, otherwise the nervous system appeared normal. The fundi were normal and the leucocytes 10,000.

For the next week the temperature was of the septic type, ranging from 99 to 103° F., and nystagmus and dizziness continued; otherwise there was no evidence of intracranial involvement.

January 31st.—The left ankle joint became very painful, red, and swollen. A blood culture was taken which showed a large number of *S. hæmolyticus*. Pron-

tosil treatment was begun next day; 25 c.c. intramuscularly was given every four hours. A second blood culture, taken next day, showed *S. hæmolyticus*. The temperature continued its septic course, ranging from 99 to 104° F.

February 4th.—The swelling about the ankle joint was subsiding and the patient feeling much better. A blood culture taken at this date showed no bacterial growth. At this point prontosil was discontinued. The next day the temperature rose to 103° F., and a fourth blood culture showed a heavy growth of *S. hæmolyticus*. Prontosil treatment was resumed.

February 6th.—Blood culture was again positive for *S. hæmolyticus*. A 500 c.c. blood transfusion was given by the citrate method.

February 7th.—The patient appeared much better; temperature 98.4° F. in the morning and 100° F. in the evening. Leucocytes, 6,400; red blood cells, 3,500,000; hgb., 65 per cent.

February 11th.—Blood culture gave no bacterial growth, prontosil was reduced to 10 c.c. daily. A second transfusion of 500 c.c. of citrated blood was given.

From February 12th until her discharge from hospital on February 27th the temperature remained normal. A final blood culture on February 17th showed no bacterial growth. In all, 665 c.c. of prontosil were given throughout the course of infection.

It is interesting to note that after the administration of 340 c.c. of prontosil one blood culture showed no bacterial growth. Prontosil

was discontinued for a short period, but the treatment resumed following the next positive culture.

CASE 2

A male, aged 44, was admitted on February 25, 1937, complaining of sore throat, inability to swallow, and swollen glands of the neck.

History of present illness.—The patient had flown from Vancouver to Montreal. On arrival he felt chilly, with generalized aches and pains, slight sore throat, and a high temperature. His fever continued for four days, after which he felt better and was up and about for three days, when he had a relapse, his temperature rising to 103° F., and he complained of a very sore throat. His condition became gradually worse until it was impossible for him to swallow even liquids.

Condition on admission.—Temperature, 102° F.; pulse, 126. The patient looked exhausted and toxic and was slightly irrational. He was unable to swallow even liquids, and had a troublesome cough due to a ropy muco-pus in the pharynx. The cervical lymph glands were greatly enlarged and acutely tender to touch. The tonsils almost met in the mid-line, the inner surface being covered with a whitish membrane. The soft palate and pharynx were acutely inflamed and oedematous. A culture from the throat showed *S. hæmolyticus*.

Treatment.—Intravenous glucose saline, 5 per cent, 1,500 c.c., was given twice a day; irrigations of Dobell's solution, and prontosil 20 c.c. intramuscularly four-hourly.

February 26th.—The treatment was continued; temperature, 100° F.; pulse, 110; feeling more comfortable.

February 27th.—Temperature, 99.2° F. There was less swelling about the tonsils and the glands of the neck were smaller and less tender. The patient was able to take 200 c.c. of fluid by mouth.

February 28th.—Temperature, 98.4° F.; pulse, 88. He was able to take fluids well. There was very little discomfort in the throat and the glands of the neck had almost disappeared. The prontosil and intravenous salines were discontinued.

In all, 200 c.c. of prontosil were given. The recovery, with the exception of the development of a frontal sinusitis, which persisted for four days, was uneventful.

CASE 3

A female, aged 22, was admitted on March 12, 1937, complaining of sore throat, inability to swallow, fever, and malaise.

Personal history.—There was a history of frequent sore throats; quinsy one year before, and scarlet fever at the age of 14.

History of present illness.—Five days before admission the patient complained of generalized pains and aches and a severe sore throat. The throat gradually became more painful and she had difficulty in swallowing even liquids. Her temperature was high, 103° F. most of the time. A culture taken from the throat showed *S. hæmolyticus*.

Condition on admission.—Temperature, 102.3° F.; pulse, 102. The soft palate was red and swollen, the uvula oedematous, the tonsils large, almost meeting in the midline, acutely inflamed, and a whitish membrane covering the inner surface. The posterior pharyngeal wall was acutely inflamed. There was a quantity of tenacious muco-pus in the pharynx which caused spasms of coughing and a great deal of discomfort. The patient was unable to swallow even liquids. She appeared to be in great distress and talked with difficulty. The anterior cervical lymph nodes were enlarged and tender on palpation. Leucocytes, 10,000; red blood cells, 3,220,000.

Treatment.—Ice bag to the throat; hot irrigations of Dobell's solution; intravenous glucose saline, 5 per cent; prontosil, 20 c.c. intramuscularly, four-hourly.

March 13th.—Temperature, 101° F. Prontosil, 20 c.c., was given every four hours and intravenous glucose saline twice a day.

March 14th.—Temperature, 103.4° F. Treatment continued; cervical glands less swollen and painful, tonsils smaller now, a fair-sized space between them. The patient was feeling more comfortable.

March 15th.—Temperature, 100.2° F.; pulse, 100. She was feeling exhausted. The prontosil and intravenous glucose were continued.

March 16th.—Temperature, 100° F. Much better and able to swallow a fair amount of liquid; much less swelling of the tonsils and soft palate.

March 17th.—Temperature, 98.4° F. The patient was taking fluids well; the swelling and tenderness of the lymph glands had disappeared; the tonsils were much less angry-looking. Prontosil was discontinued.

Until her discharge on April 23rd the temperature remained normal, and the patient made an uneventful recovery. In all 230 c.c. of prontosil were given.

One cannot but feel after treating these patients that prontosil played a major part in their rapid recovery.

In patients 2 and 3 the routine, accepted methods of treating septic throats had been rigorously carried out before entering hospital, and their rapid recovery and feeling of well-being following the administration of prontosil were almost dramatic.

METHYL CHLORIDE (REFRIGERATOR) GAS POISONING: AN INDUSTRIAL HAZARD.—The appearance of two new cases of methyl chloride poisoning that Weinstein observed emphasizes the fact that this industrial danger still exists. His patients were two white men, aged 44 and 28 years, engaged in repairing an air conditioning plant located in the basement of a business concern. Ventilation was poor but considered adequate. After two hours of work the older patient noted headache, dizziness and fatigue. He accordingly quit work. The younger man continued to work an additional two hours, at the end of which time he too was forced to stop. Methyl chloride gas was the cooling agent used in the air conditioning plant which these men repaired. This

gas has many advantageous features besides its low boiling point (−23.7° C.); it is stable, non-corrosive to metals, relatively non-inflammable, non-explosive, non-injurious to foods, furs or textiles, and may be used in low pressure systems. Unfortunately the gas is absolutely non-irritating and practically odourless. Thus the victim of exposure is poisoned without warning. It is apparent that the ideal refrigerant has not been discovered. The experience with the patients reported herein indicates that supervision of installation and operation of refrigerating plants is not universally practised. It is desirable that the hazards of mechanical refrigeration should come under the supervision of official public health agencies.—*J. Am. M. Ass.*, 1937, 108: 1603.

FATAL AIR EMBOLISM—CASE REPORTS*

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DEATH from air embolism, while not at all common, occurs occasionally, and cases of air embolism with recovery are probably more common than is generally thought. Death when it occurs is apt to come with tragic suddenness, and since manifestly experimental work on the human subject is impossible, and that on animals not necessarily comparable with what occurs in the human subject, our knowledge of the phenomenon and of its mechanism has progressed very slowly, in spite of the fact that the damaging effects of the introduction of air in quantity into the circulation have been recognized for two hundred years or more.

In 1667 Ride noticed that the introduction of air in large quantities into the veins of animals resulted in death. In 1818 Beauchesne recorded a death from air embolism following an operation on a tumour of the neck, and since then operations of any magnitude in the neck region have been considered to be especially prone to the occurrence of air embolism. Cases have from time to time been reported during the last century, and during the past 15 years more and more cases are coming into the literature, and animal experimentation is being brought to bear on the subject. Chase,¹ in reporting a fatal case of air embolism from the entry of air into the pulmonary vein during lobectomy, demonstrated embolism of the smaller capillaries of the brain with extravasation of blood round some of them. Experiments on rabbits, with a study of the mesenteric capillaries, led to the conclusion that mechanical as well as neurovascular changes in the arterioles were important factors. Wolffe and Robertson,⁷ in experiments on rabbits and dogs, concluded that the lethal dose for rabbits was 0.5 c.c. per kilo, while for dogs it was 15 c.c. per kilo, and that the air acted in a mechanical way by blocking the pulmonary artery and its branches and finally the right heart. Of course, it is perhaps not sound to conclude that what

holds for one animal will hold for another or for the human subject.

Air may enter the pulmonary circulation in the course of operations involving the pleura or lung, or in the production of artificial pneumothorax. What used to be called pleural shock is now thought in many cases to be a mild degree of air embolism. Relatively small amounts of air in the pulmonary circulation may be fatal. The air proceeds through the pulmonary vein to the left auricle and left ventricle, from where it may escape to the cerebral arteries, coronary arteries or peripheral arterioles. Blocking of the cerebral arterioles results in transitory paraplegias which may persist for varying periods. Ischæmia of cerebral tissue results, and if this ischæmia persists for more than fifteen hours there may be death of cerebral tissue. Blocking of the coronary arteries leads to ischæmia of the heart muscle and to cardiac failure, with the heart in systole. Whether this ischæmia may lead to infarction of the heart muscle is not known. Resuscitation in these cases must be brought about in less than seven minutes or death will ensue. Blocking of peripheral arteries may lead to blanching of skin areas, and cases of transitory blindness due to the presence of air in the retinal arteries are recorded.

More commonly, however, air enters the peripheral venous circulation. This was early observed in the case of wounds of the jugular vein, and has been noted as an accident in the course of thyroidectomy. Fatal cases of air embolism have been reported from the dilatation of the bladder with air in cases of tumour or ulcer which leave veins open. Also, and the cases here presented illustrate this mode of entry, air may enter the uterine sinuses in the course of attempts at abortion,^{8,9} with fatal results. One case is reported, which ended fatally, from therapeutic insufflation of the vagina for trichomonas infection.¹⁰ The introduction of a sufficient amount of air at any of these entry points results in its accumulation in the pulmonary artery and its branches, and finally in the right heart, after which death

* A paper read before the Academy of Medicine, Toronto, on November 23, 1936.

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occurs often with startling rapidity. The effect of a patent foramen ovale on the distribution of air in these cases must be kept in mind.

CASE 1

R.C., female, unmarried, aged 24 years, visited an apartment between 2.00 p.m. and 4.00 p.m. on June 17, 1932. A physician was called at 3.50 p.m. and found her dead. She had previously been in good health.

An autopsy was performed two hours after death. The face was ashy grey in colour. The abdomen was prominent, and a fluctuant tumour could be made out. Internal examination showed the presence of a fetus of seven months. The placenta was partially separated and showed some hæmorrhage between it and the uterine wall. The space showed also the presence of air bubbles. The cervix was dilated to the size of one finger. The uterine wall crepitated, the sinuses being filled with froth. Air was found in the uterine and iliac veins and in the inferior vena cava. The right auricle was dilated and both auricle and ventricle were filled with frothy blood. A few bubbles were seen in the cerebral vessels. There was no evidence of *Cl. welchii* infection on culture. Cause of death—air embolism, from air introduced into a pregnant uterus.

CASE 2

W.B.K., female, married, aged 35 years. On August 9, 1933, her sister who lived in the house with her heard cries of distress, went to her room, and found her dying. In the room she found a pan of boracic acid solution and a Higginson syringe. Her sister stated that she had made a previous attempt to procure an abortion on herself. An autopsy was performed 24 hours later, the body having been embalmed in the interval. The uterus was a pregnant one at about 3½ months. The fetus and membranes were absent. The uterine wall contained air; there was air in the inferior vena cava, and both chambers of the right heart contained air and bloody froth. In this case, apparently, the previous attempt at abortion had been successful, and the second attempt, to make assurance doubly sure, resulted in death from air embolism. Cause of death—air embolism from air introduced into the uterus.

CASE 3

M.L., female, married, aged 20 years. On October 8, 1933, a physician was called to her house and found her dead. In the room were found a Higginson syringe, two basins smelling of lysol, and a bottle of lysol. The evidence showed that she was alive at 5.20 p.m. and was found dead about 6.00 p.m. by the doctor. Autopsy was performed three hours later. The uterus contained a fetus of about 3½ months. The cervix was partially dilated, and about half the placenta had been separated from the uterine wall. The space contained a blood-tinged fluid smelling of lysol. The uterine wall was crepitant and contained air in the sinuses. There were bubbles of air in the uterine and iliac veins and in the inferior vena cava. The right heart was crepitant, and both chambers contained a bloody froth. The pulmonary artery contained a frothy blood. Cause of death—air embolism from air introduced into a pregnant uterus.

CASE 4

D.J., female, aged 23 years, unmarried. On February 15, 1936, at 2.30 p.m. the ambulance was called to a house and brought the body of the deceased to the hospital. She was dead on admission. Evidence showed that she had gone to the house about 2.00 p.m. In the house were found pans smelling of lysol and the charred remains of a Higginson syringe taken from the stove. Evidence showed that an intra-uterine injection of lysol had been undertaken, and that the subject had collapsed and died within about 15 minutes. Autopsy was per-

formed about four hours later. On incision of the anterior chest wall, bubbles of air could be expressed from superficial and deep veins, although there was no crepitation in the tissues. The heart crepitated on palpation. The uterus contained a fetus of about 4½ months, being dead apparently about 48 hours. There was a separation of the placenta showing considerable necrosis, and an area of fresh separation showing slight hæmorrhage. The uterine sinuses and veins contained air bubbles and froth. There was air in the iliac veins, and in the inferior vena cava. The right auricle and ventricle were filled with froth, as were the pulmonary artery and its branches. There were bubbles of air in the coronaries and some in the cerebral vessels. Cultures failed to show the presence of *Cl. welchii* in any of the organs. Cause of death—air embolism from air introduced into a pregnant uterus.

These four cases illustrate air embolism produced in attempts to procure abortion, and it is this type which the gynaecologist and medico-legal worker are most likely to meet. In three of these cases the air was known to have been introduced by means of a Higginson type of syringe, and in the fourth case its use was suspected but could not be proved. The Higginson syringe lends itself admirably to the production of air embolism. If the receiving tube inadvertently comes out of the pan holding the solution, one or two bulbfuls of air is probably all that is necessary to provide enough air to fill the pulmonary artery and its branches with air, and then to fill the chambers of the right side of the heart with a bloody froth. When this condition obtains death is only a matter of minutes, and in all four cases it was established by evidence that death ensued in a very short time after the presumed introduction of the air and its application to the gaping uterine sinuses. Case 4 varies from the others in that there appeared to be air in the peripheral venous circulation and to a small extent in the coronaries. The explanation of this is not quite clear. Whether in the exertion of the embarrassed heart some air was driven through the pulmonary alveolar walls, or whether a more than ordinary amount of air was absorbed into the blood, to be released in gaseous form as the temperature dropped, or whether the relative incompetence of valve leaflets working on froth instead of fluid blood allowed some back flow of air which by gravity arose to the upper part of the body after death is a matter of conjecture. In this case, also, the evidence of a previous attempt at abortion with consequent necrosis of tissue called for much bacteriological work on the organs to rule out the possibility of *Cl. welchii* infection. Careful autopsy technique is

necessary in cases where air embolism is suspected. The heart, coronary arteries and cerebral vessels require the most careful scrutiny. Palpation of the heart will, of course, by the detection of crepitation, give one much evidence, but the heart should always be tied off and opened under water to demonstrate without doubt the presence of air in the chambers or coronary arteries. Some authorities recommend that the brain should be removed under water, with the same object in view. It must be said that in removing the skull-cap it is easy to tear meningeal vessels and admit small amounts of air to them, so that extreme care should be exercised in this regard. The question of *Cl. welchii* infection must always be ruled out by bacteriological methods, and to this end autopsy should be carried out as soon after death as is reasonably possible. Having in mind these precautions, the anatomic picture of death from air embolism is striking and pathognomonic and not easily mistaken after one has seen a typical case.

It is a matter of common knowledge that small amounts of air may be liberated in the circulatory system without untoward effects, and that even larger amounts, administered slowly, do not cause serious if any trouble, although Wolffe and Robertson,⁷ working with rabbits and dogs, felt that the speed of injection made little difference, air embolism resulting when the injection time was shorter than the absorption time. Tolerance for air varies markedly in animals, and undoubtedly varies equally markedly for the human subject. The amount required to produce a fatal air embolism when introduced into the peripheral venous system is, no doubt, governed to some extent by these factors, but when the amount is sufficient to fill the pulmonary artery and its branches, and finally the right heart, death must ensue with considerable rapidity. The increase in the volume of the introduced air consequent upon its being raised to body temperature must be kept in mind. A very much smaller amount of air introduced into the pulmonary circulation may cause death through coronary or cerebral thrombosis. Death probably comes in marked rapidity in the majority of cases of air embolism, where the air is introduced into the peripheral venous system, whereas in many cases where air enters the pulmonary circulation death is apt to ensue more slowly.

The cause of death, which in fatal cases usually comes with startling suddenness, has been assigned to various factors. In embolism of the cerebral arteries and of coronary arteries, it may well be due to ischæmia of the brain or heart muscle, with failure of function. In cases such as those here presented it is probably due to several factors. There is first the actual mechanical block to the circulation, which must soon result in a fatal anoxæmia. There is the factor of cardiac ischæmia arising from this. The activity of heart muscle on froth instead of liquid blood probably sets up a fibrillation of the muscle. The stretching of the pulmonary vessels may introduce the element of shock, as is seen in cases of pulmonary thrombosis. In all probability these and possibly other factors enter into the dramatic suddenness with which death comes in these cases.

The most vexed question in connection with fatal air embolism, at least, in so far as the medico-legal aspect of the subject is concerned, is the degree of physical activity possible in the subject between the time of the introduction of the air and its fatal ending, and the length of this interval. In cases of abortion the rapidity of the ascent of the air from its position between the separated placenta and the right heart seems to me to be the important factor, and of course, this factor is difficult to estimate in any given case. Where the sinuses exposed are not unduly large it is quite possible that the conduct of the air upwards may be delayed, and, during this period of delay, it is quite conceivable that the patient might be able to carry on activity and even to walk some distance. But from the moment that the pulmonary artery becomes filled with air and the right heart begins to convert the mixture of blood and air into an elastic froth I cannot believe that much activity is possible. The factors of asphyxia and anoxæmia which must very soon thereafter become operable, together with the element of shock probably attendant upon the stretching of the pulmonary artery and right heart, must prohibit any very considerable or prolonged physical exertion and death must ensue rapidly thereafter. But I presume the period of delay before this occurs might be sufficiently prolonged to permit of it, and, as said previously, this time factor would be difficult to estimate.

In conclusion, it may be said that while the dangers of the introduction of air in any

quantity into the circulation have been known since the seventeenth century cases of death resulting from this cause seem to have increased during the past decade, especially in connection with criminal abortion. Air embolism is of two types, that resulting from the introduction of air into the pulmonary vein or its branches, in which case death, if it results, comes gradually, due mainly to embolism of cerebral arteries; and that resulting from the introduction of air into veins of the long circulation, especially those of the bladder and uterus, in which case, if the amount of air be sufficient, death occurs with tragic suddenness after the pulmonary artery and right heart become filled with a mixture of air and blood. The time required to produce a fatal result probably varies with each individual case, and the physiological factors

involved may be cerebral ischæmia, cardiac ischæmia with failure, or asphyxia and anoxæmia, with the possibility of all three being contributory.

REFERENCES

1. CHASE, W. H.: Anatomical and experimental observations on air embolism, *Surg. Gyn. & Obst.*, 1934, 59: 569.
2. DURANT, T. M.: Occurrence of coronary air embolism in artificial pneumothorax, *Ann. Int. Med.*, 1935, 8: 1625.
3. HAMILTON, C. E. AND ROTHSTEIN, E.: Air embolism, *J. Am. M. Ass.*, 1935, 104: 2226.
4. JACKSON, C. AND BABCOCK, W. W.: Pleural shock, *Surg. Clin. of N.A.*, 1930, 10: 1265.
5. LARSON, L. M. AND NORDLAND, M.: Air embolism complicating thyroidectomy, *Ann. Surg.*, 1934, 99: 112.
6. MATHE, C. P.: Fatal embolism due to inflation of bladder with air, *Surg. Gyn. & Obst.*, 1929, 48: 429.
7. WOLFFE, J. B. AND ROBERTSON, H. F.: Experimental air embolism, *Ann. Int. Med.*, 1935, 9: 162.
8. PARRY, L. A.: Criminal Abortion, Bale, Sons and Danielson, London, 1932.
9. HAMILTON, I.: Sudden death due to air embolism, *Med. J. Australia*, 1936, 11: 789.
10. PEIRCE, S. J. S.: Death from vaginal insufflation, *Canad. M. Ass. J.*, 1936, 35: 668.

SUPPORTING PALATINE PROSTHESIS CONSECUTIVE TO THE REMOVAL OF BENIGN TUMOURS OF THE PALATE*

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OF all authors who describe the treatment of benign palatine tumours, some advise the removal by means of an incision, and then suturing of the wound; others prefer simply to let the wound heal by granulation without coaptation after the operation. Nowadays the surgeons are forced to admit, especially since the Great War, that in the presence of a fracture of the maxillæ we must have recourse to collaboration with a dentist for a prosthesis, in order to obtain the best possible results. Inspired by this fact, tested out in many instances while chief of service to the military hospitals of St. Cloud and of St. Ouen, France, where I treated, from 1915 to 1918, numerous maxillo-facial wounds, I thought that this same collaboration should exist after the removal of benign tumours of the palate. Indeed, if we practise a median incision over the neoplasm, and after having taken it away we suture the lips of the section, there inevitably remains an empty space which becomes full of blood. Because of the fact that there exists a considerable

microbian flora in the mouth the slightest infection of the operative field may be terminated by suppuration of the hæmatoma. If, on the contrary, the removal of the tumour is done after incision without consecutive sutures, the wound infects itself, and the cicatrization is therefore produced very slowly. Also, during this lapse of time, the patient is submitted to numerous inconveniences. In so far as the process which consists in practising two elliptic incisions at the base of the neoplasm and in removing this with its covering tissue is concerned, I consider that this method is not worthy of modern surgery and should never be employed.

The combined technique that I recommend has for its object to remove the tumour after a median incision; to make two or three sutures in order to allow coaptation; and then to apply a supporting palatine prosthesis. It is easy to conceive that this process offers the best prognosis for a rapid cure without inconvenience to the patient. Here is furthermore an observation in support of this new method.

CASE REPORT

Mr. P.R., aged 23 years, was sent to me for a small tumour in the roof of the mouth. He relates that about a year ago, the right side of his palate started to

* Read before the "Congrès de l'Association des Médecins de Langue Française de l'Amérique du Nord", Montreal, September 7 to 10, 1936.

increase in volume. He never received any traumatism of the mouth. Two physicians consulted, before coming to me, practised tappings which produced no results. During this period the only treatment had consisted in antiseptic gargles.

On examination of the mouth, I observed an oblong tumour of about three centimetres in length, and two and one-half centimetres in width, the centre of which was opposite the second upper molar on the right side. It was in contact with this tooth, and terminated at the median raphe of the palatine vault. The tumour was glistening. The tonsils and the rhino-pharynx were normal. There existed a slight spur to the right of the septum.

I proposed an operation which was accepted. However, before the intervention I asked Dr. L. P. Reeves to make me a prosthesis, discounting in advance the normal anatomy of the palate after the removal of the tumour. My friend consented to take charge of this delicate work, and furnished me with following information.

"An impression of the palatine vault and teeth had been taken in compound, and a model was poured in cœcal. This model reproduced a tumour invading the region between the upper right second molar, and the median line extending from the second bicuspid to the third molar on the same side (see Fig. 1).

"The protuberance on the model was completely removed in order to show a normal palatine vault. A prosthetic piece in vulcanite covering this palatine

vault was then constructed as if the tumour had never existed. This mobile prosthesis was made in one piece adapting itself to the palate, and was held in position by three chromel clasps encircling three teeth in order to secure stability (see Fig. 2).

"A prosthesis of this type must be perfectly adapted to the tissues without exercising any compression. The surgeon must discount that the piece will not prevent drainage, always necessary after the intervention. Four holes had therefore been drilled in the appliance opposite the tumour."

In possession of this prosthetic piece, I operated on March 21, 1935.

Operation.—Local anaesthesia with novocain-adrenalin. Incision of three centimetres over the middle part of the tumour, parallel to the superior dental arcade to the right. The removal of the neoplasm was particularly easy, on account of the fact that I could cleave it without any appreciable hæmorrhage. I applied two silk sutures over the lips of the incision, to maintain the coaptation, and immediately afterwards placed the prosthesis which fitted the palatine vault perfectly. The three clasps encircling the three teeth maintained it in a good apposition.

Post-operative sequelæ were very simple, and the prosthesis was removed from time to time to allow the asepsis of the mouth by means of rinsing. From the fourth day the incision was already so solid that I removed the stitches, counting on the prosthesis for future support. The patient left the hospital perfectly cured at the end of eight days. He was seen again seventeen months later. The cure remained permanent, and the operative cicatrix was hardly perceptible.*

Dr. Simard, who made the anatomo-pathological examination of the neoplasm, gave me the following report.

The tumour is largely necrotic and dissociated in its centre. The living peripheral tissues are of an epithelial and conjunctival nature.

The epithelial elements sometimes form glanduliform tubes heaped up the one against the other, at other times characteristic malpighian strands with filaments of union. Here and there, in the centre of some malpighian strands appear cavities surrounded by cubical or prismatic cells.

The conjunctival element is represented by sclerous or fibro-hyalin islets in continuity sometimes with the epithelial formations.

The histological picture is one of a mixed tumour of a salivary gland.

There is nothing to add to this communication, which has for its object to point out the importance of the collaboration with the dentist for the preparation of a well-designed prosthesis previous to the removal of benign tumours of the palate. Though the neoplasm may be a mixed tumour of salivary gland, a neurinoma, or what-

* This patient was presented at Notre-Dame Hospital, at the time of the "Congrès de l'Association des Médecins de Langue Française de l'Amérique du Nord", September 10, 1936.

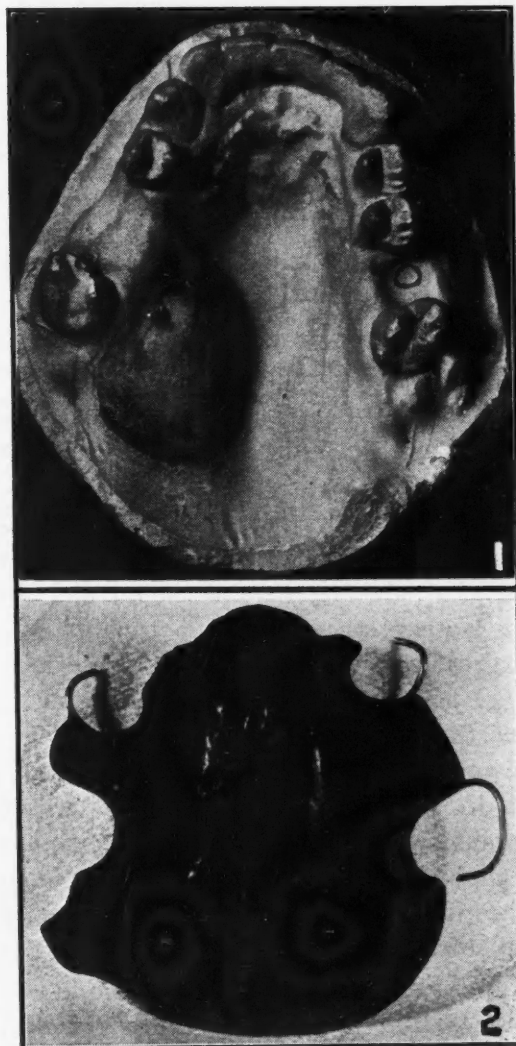


Fig. 1.—Benign tumour of the palate.

Fig. 2.—Supporting palatine prosthesis.

ever non-malignant neoformation, it is always true that an apparatus of support is indicated after an operation. If, instead of a benign tumour, we are in the presence of a cancer, the line of conduct for the treatment can be determined only after a consultation with a radiologist, to judge of the advisability of x-rays or radium, associated with or without surgery.

With the apparatus that I recommend, it is easy to understand that after having removed

the neoplasm—whatsoever may be its volume—and having placed points of suture on the lips of the incision, the cure must necessarily be evolved under the best possible conditions. Indeed, the prosthesis has for its object to push the dissected tissues towards the depth, and consequently to prevent the formation of an hæmatoma, to forestall infection, and finally to hasten the cure, all things which are much more difficult to obtain with other operative methods.

HAY FEVER: THE DIAGNOSIS AND TREATMENT*

By A. N. HARDY

Regina

“HAY fever” so-called, or, better, “seasonal allergic rhinitis”, is a term applied to a syndrome produced by exposure of the individual to plant pollen at a certain season of the year. It is characterized by a hypersensitivity of the mucous membranes of the nose and throat to specific pollens when inhaled through the nose. The diagnosis of hay fever is based on the history of the occurrence, the symptoms, and the clinical findings.

Hay fever occurs during the season of pollination, which is chiefly during the months from April to October. The determination of the flora of a locality and the time of pollination will assist materially in ascertaining the type of pollen to which the person is sensitized. A particular time of occurrence suggests that certain kinds of pollen are the cause of the symptoms. In this way a great majority of the pollens can be eliminated, and skin tests made for only those particular pollens that are known to be present at that time of the year, *e.g.*, a patient with hay fever during the early summer would not obtain results by treatment for ragweed, which flowers late in the fall, even though the skin test gave a positive reaction to ragweed.

The hereditary factor plays an important part in the diagnosis of hay fever. Cook and Vanderveer in a study of 504 cases of hay fever and asthma reported a family history of allergy in 48 per cent.

SYMPTOMS

The onset of symptoms is heralded by an attack of sneezing and a watery discharge from the nose. The attacks are usually transient at first but they gradually recur more often and are more severe. There is itchiness and congestion of the mucous membranes of the eyelids as the disease progresses. The discharge from the nose becomes more profuse and is always of a thin, watery consistency. Often the nostrils become completely blocked. The patient complains of a feeling of heaviness in the head. In a large proportion of severe cases he develops a cough and symptoms of asthma supervene.

The skin around the entrance to the nostrils is red and sometimes excoriated from the irritation of the profuse secretion. The mucous membranes of the nose are markedly oedematous, of a pale greyish pink colour and bathed in a watery secretion. The turbinate bones are greatly swollen, boggy and pale looking. Polypi may sometimes be seen hanging down from the region of the ethmoid cells. The pharynx and larynx may become red and congested. Examination of the nasal secretions shows the presence of a large number of eosinophile cells, and section of the submucous tissue will reveal eosinophile infiltration, a characteristic symptom of nasal allergy.

Hay fever may be mistaken for acute rhinitis in the initial stages. In acute rhinitis the symptoms are more acute at the beginning and more sustained and disappear in a few days.

* A paper somewhat abbreviated from one read before the Saskatchewan Medical Association, September, 1936. The bibliography can be obtained from the author.

The discharge is more of the muco-purulent variety. In hay fever, in the early stages, the attacks are more or less intermittent, gradually becoming more frequent and more prolonged and extending throughout the whole season of pollination. Spasmodic sneezing with profuse watery discharge, itchiness and swelling of the eyelids with the presence of eosinophilia in the nasal secretions are characteristic of the disease. The clinical diagnosis can usually be verified by positive skin reactions to the offending pollen.

The various methods of testing with pollen extracts are well known and will not be dealt with here.

It may be said, however, that the cutaneous or dermal tests have their greater sphere of usefulness in testing children, who react better than adults, and patients sensitive to air-carried substances such as turpentine, benzol, etc., which prove harmful when injected subcutaneously. In the intracutaneous method the same extracts used in testing may be used for treatment. The principal advantage of the scratch method over the intracutaneous is its greater safety from constitutional reactions. The intracutaneous method can be performed more quickly and the tests read sooner.

Recently an intramucosal test has been tried by Dean and Lintons and has been found more sensitive than other tests. It is performed between attacks. The anterior end of the inferior turbinate is swabbed with a 1 per cent cocaine solution, and a minute quantity of the extract injected superficially beneath the mucous membrane. Sometimes a drop of blood follows the needle which is removed. Positive reactions are characterized by oedema in the region of the injection. Sometimes a wheal is noticed and considerable swelling and nasal obstruction with increased secretion follows. Reactions usually occur in 15 to 30 minutes and may remain for several hours. It has certain disadvantages. Only two tests can be performed at a time, on the other hand these authors state the information is more reliable as to the sensitizing proteins.

TREATMENT

The successful treatment depends on the knowledge of the various factors which enter into the production of the disease. A thorough examination of the patient should be made to ascertain if possible the causative agents. Any hereditary predisposition should be noted. General examination, including gastro-intestinal and liver functions, is important. Frequently a pollen hay fever is complicated by a food or other allergy, producing a toxicosis, asthma or other complications. Local examination of the

nose and sinuses is of prime importance. The treatment of hay fever has in the majority of cases been unsatisfactory so far as a permanent cure is concerned.

The treatment of hay fever may be dealt with under the following main divisions.

(1) *Removal of the exciting cause*—change of climate, air-filtration, etc. (2) Specific desensitization by the administration of pollen extracts. (3) General systemic—dietetic, physiotherapy, drugs, etc. (4) Local, including treatments to the nose, throat and sinuses.

Only one form of treatment offers a sure and permanent cure and that is a change of climate to a place free from the sensitizing pollen. The patients invariably get well as soon as the sensitizing substance is removed. The method of air-filtration has been used by various men with good results in some cases (Crip and Green).

Specific desensitization includes treatment with vaccines made from the pollen to which the patient is sensitized. The mechanism by which desensitization takes place is unknown, nor can it be stated that definite desensitization takes place, because even after a patient is cleared of his symptoms by vaccine therapy the skin test may remain unchanged.

According to Sterling the causes of failure in the treatment by desensitization are: improper preparation of pollen extracts; inconsistent standards of measurement; no preparation on the market has sufficient material for correct desensitization. Most manufacturers recommend the use of a 1 per cent solution, which is not sufficiently strong.

Brown makes his dilutions from a 10 per cent extract. All treatments are injected subcutaneously, keeping the patient quiet for 15 to 30 minutes following the injection of the stronger doses, which aids in preventing constitutional reactions. He avoids giving too strong doses during the hay-fever season, as the patient is inhaling considerable pollen from the air and there is danger of a constitutional reaction. He begins about three months before the season and works up gradually, giving a treatment every four to seven days until he is giving 50,000 to 200,000 units before the season. During the season he either decreases the dose or suspends treatment altogether when the patient has received large enough doses for im-

munization. He concludes by stating that none of his patients had hay fever the previous year with the exception, in some cases, of transitory symptoms. He says that treatment with maximum doses seems to be the best method of securing complete and permanent freedom from pollen asthma and hay fever. In many cases this is a long and tedious process but the results are so uniformly satisfactory that they more than justify the time and trouble required. Three types of treatment are adopted: (1) the pre-seasonal; (2) the co-seasonal; (3) the perennial.

The pre-seasonal usually starts about three months before the time in the year that the patient is attacked, with gradually increasing doses at three or four days intervals, working up to 7 day intervals. Twenty to 25 injections are usually given before the hay fever season. The co-seasonal treatments are given during the time of the disease. Vaughan has been able to accomplish more with very small doses carefully administered. Some workers use only the co-seasonal treatment, giving the injections intracutaneously in small doses. Phillips in a group of 322 cases had satisfactory results in 91 per cent of cases by this method. The perennial treatment consists in continuing the treatment throughout the whole year for an indefinite period, giving the maximum dose at two to four week intervals. Hansel quotes Vaughan, Figley, Brown and others to the effect that the perennial form of treatment offers the best results.

Constitutional reactions are characterized by a sudden onset of sneezing, coughing, urticaria, asthma or an exaggeration of the patient's condition. Adrenalin is the specific drug for this condition, given in 5 to 15 minim doses, subcutaneously or intravenously. Part of the adrenalin may be injected into the site of the skin reaction; a tourniquet may be placed above the site of the injection and the patient kept in a reclining position.

The results of specific pollen therapy vary greatly with different authors. Shahan reports in 1929 that out of 104 cases treated at the Clinic 80 could be considered successfully treated. He states: (1) ragweed hay fever is more resistant to treatment than the vernal type; (2) patients showing the highest grade of sensitization gave the best results; (3) no permanent

desensitizations have been attained by the pollen therapy; (4) hay fever complicated by asthma offers less encouraging results; (5) constitutional reactions occur in about 1 per cent of doses given; adrenalin should always be on hand; (6) the dosage varies with the individual sensitivity.

Vanderveer in 1935 gives more encouraging results from the desensitization method. He states that permanent results can be expected from specific pollen therapy in over 50 per cent of all cases. His results were as follows in 159 cases treated.

	Percentage	
Cured	31	or 20
Greatly relieved	53	or 33
Decidedly	21	or 13
Hay fever as severe as before treatment	54	or 34
Total	159	100

These figures compare favourably with other authorities. Under proper treatment a considerable percentage of permanent cures do occur.

Of the various treatments for hay fever recommended, *general systemic treatment*, including diet, physiotherapy, exercise, etc., has not received the attention it should.

Cameron states that "basic toxicosis" is the primary factor in all forms of allergy, as evidenced by the fact that even after the end of the desensitization treatment the skin reaction is little altered. He says that abnormal bowel and liver activity bring about a disturbed metabolism resulting in an overproduction and faulty elimination of waste products with a resultant toxicosis; that the basic cause of all is an intestinal toxicosis, and this toxicosis is of an acidosis type as shown by blood and urine; that allergy is a product of the toxicosis. He considers the best form of desensitization for hay fever and asthma is by detoxication, which treatment consists of colon lavage (with two gallons of plain water daily) mild aperients, physiotherapy, exercise and diet to eliminate the toxins and establish adequate body metabolism. His diet is divided into two classes. During detoxication it consists of the mono type, or the more liberal but eliminating diet of fruit and vegetables, with copious fluids between—several glasses of orange juice. The diets continued until by clinical observation and laboratory findings the patient is detoxicated, about

four weeks is required, when a more liberal diet with protein carefully added is substituted.

Pollen peptone therapy.—Recently Urbach has been experimenting with specific types of pollen peptones produced from blooming grass gathered just before the pollen is scattered. With this substance good results were obtained in 75 cases. Morning and evening the patient is given 2 g. by mouth on an empty stomach of the peptone from the pollen to which the person is sensitized. He calls the treatment "mixed blossom peptone therapy". A. G. Auld, in 1917, began to advocate the use of non-specific peptone therapy, and states that Witte's new peptone treatment gives good results and is devoid of the toxic effects of the ordinary peptone.

Auto-serum therapy.—This, first originated by Flandin, consists in withdrawing some blood from a patient and reinjecting the serum subcutaneously. A. F. Wright comments on the treatment of hay fever by this method. His results were complete relief for one year. He states that Flandin's method is equally effective in allergic and acute septic infections, but its action is only transitory and must be replaced by more permanent methods of stimulating resistance by appropriate antigens. E. Joltrain states that the intravenous injections of auto-serum which appear to be effective so often in asthma do not appear to him to produce more than 10 per cent of favourable results in hay fever.

Bacterial vaccines have been extensively used, either alone or in conjunction with the administration of pollen extracts, with good results in cases complicated by asthma.

Viosterol in the treatment of hay fever.—In 1933 Rapport, Reed, Hathway and Struck treated 212 patients of hay fever and asthma with viosterol of high potency from 2 to 10 minims daily of 10,000x (1 c.c. of viosterol 10,000x contains 920,000 international units of vitamin D). Of the 212 patients 68 received viosterol alone with definite relief in 82.4 per cent. One hundred and forty-four cases received viosterol and pollen combined with relief in 96.5 per cent of cases. It was concluded that the treatment with viosterol and pollen combined was much more effective than either alone.

The relative value of *histamine* and *typhoid protein* for the control of asthma and hay fever is reported by Thiberge. He states: "The prompt termination of asthma after intravenous injections of standard triple typhoid vaccine by various workers caused the author to use typhoid bacilli for the preparation of the antigen used in his series of cases."

The author concludes as follows. Typhoid split-protein and histamine are both useful in the treatment of allergic cases, be they skin, respiratory, bacterial or digestive. Typhoid split-protein is much safer than histamine though not so rapid nor so powerful in its effect. Small intradermal doses will work better and more safely than large doses. Histamine in the aged should be used with caution in minute doses.

Drugs.—The internal administration of *nitrohydrochloric acid* in large doses has been reported by Beckman who has used it extensively with very satisfactory results. He states that relief in the majority of cases is almost immediate. He considers the treatment fully as effective as desensitization.

Intranasal treatment.—The first thing to do at the outset of all intranasal treatment is to correct any nasal deformities and establish proper ventilation of the nose and accessory sinuses. In case of a deflected septum or undeveloped narrow nostrils with a thickened septum a resection of the septum is imperative. It is remarkable what a relief is experienced when the nasal obstruction is relieved.

Operations on the sinuses have in the main been disappointing in hay fever. So often the question arises whether the case is one of genuine sinus infection or a hyperplastic condition secondary to and caused by the nasal allergy. These hyperplastic conditions often show by x-ray a marked thickening of the mucosa of the antra and slight haziness of the ethmoids. On washing the antra they are usually found clear or to contain a slight amount of clear mucus. Inspection in the region of the ethmoids reveals swelling of the mucous membranes and sometimes polypi but no pus. In these cases operation on the sinuses, I have found, does no good and may even aggravate the condition. In cases of purulent sinusitis the operation is warranted on the grounds of increased toxicity produced by the

focal infection. In such cases marked benefit is often noted by a thorough cleaning out of the infected area.

Of the special intranasal treatment the one method that I have used for the past fifteen years, which has given me more satisfactory results than any other, is *cauterization* with the electro-cautery of the sensitive points of the nasal mucous membranes. It is a well known fact that all cases of hay fever exhibit a hypersensitiveness of the nasal mucous membrane. Tactile sensibility is markedly increased. This no doubt is in a measure due to the neurotic element in the case and also to pathological conditions in the nose producing a continuous irritation. Bearing in mind the sensory nerve supply, the anterior nasal, a branch of the ophthalmic, and branches from Meckel's ganglion, we first with a cotton-tipped probe locate the sensitive nerve endings around the anterior and of the inferior and middle turbinates and the tubercle of the septum. These areas are thoroughly anæsthetized and the galvano-cautery lightly applied. The area on the outer wall extends from the lower anterior border of the inferior turbinate anterior to and upwards for about $\frac{1}{4}$ inch above the middle turbinate. The tubercle is at the anterior upper portion of the septum. One or both nostrils may be operated on at one sitting. I can state from fifteen years' experience with this method that in hay fever, uncomplicated by asthma, cauterization gives immediate and marked relief in nearly 100 per cent of cases. A considerable portion of cases, especially when combined with a submucous resection to relieve obstruction and give free ventilation, are permanently cured. In other cases they have no serious trouble other than an occasional sneeze during the hay-fever season. In some of these cases I have performed a mild secondary cauterization with still further beneficial results. To insure success the treatment should be applied lightly but extensively enough to cover the hypersensitive areas. No complications have occurred as a result of the treatment in any of my cases even though most treatments have been given when the disease was at its

worst. A number of other operators have reported favourably on this method.

Treatment of hay fever by ionization.—Treatment of hay fever by ionization to the nasal mucous membranes, first introduced by Demetriades of Vienna more than ten years ago, is being extensively employed by various workers, using Warwick's method. Warwick reports 40 cases with complete relief in 39. He lays great stress on the technique in order to secure results. He claims that the action of the ionization is a systemic one, producing a chemical change in the person ionized rendering him less sensitive to substances to which he previously gave definite allergic manifestations. Proof of this is his work on certain cases of food allergies manifested by urticaria and asthma and cases of angio-neurotic oedema who had never complained of nasal symptoms. Hansel commenting on this method, states: "The relief of other manifestations of allergy such as urticaria, *e.g.*, by this method, would suggest that there is also a general desensitization." Alden summarizes the results of 700 bilateral ionizations by several rhinologists for the treatment of hay fever and asthma. In 416 cases of uncomplicated hay fever complete relief was obtained in 63 per cent, 75 per cent of the cases obtained 80 to 100 per cent results. Complete failure occurred in only 8 per cent. On the other hand, Ramirez in a study of 75 cases, states that 25 cases were non-specific vasomotor rhinitis and these showed definite evidence of improvement. The other 50 cases of true seasonal hay fever cases received no benefit from the ionization treatment, and he concludes by saying that intranasal ionization for hay fever has no merit.

Other methods of local treatment include injections of alcohol, 60 to 70 per cent, into the inferior turbinates, swabbing the mucous membranes with pure carbolic acid, local radium and x-ray therapy, endonasal irradiations with ultraviolet light, and other forms of local treatment, but none of these methods have in my opinion been sufficiently investigated to warrant their recommendation.

INTESTINAL OBSTRUCTION DUE TO GALL STONES

BY CLARENCE A. RYAN, M.D., C.M.

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A REVIEW of the literature on this subject shows that, while a considerable number of cases have been reported, the condition is comparatively rare. In 1925, the British Medical Association reported 3,066 cases of intestinal obstruction, 28 of which were due to gall stones;¹ 14 of these 28 terminated fatally. Wagner² collected 334 cases of obstruction due to gall stones up to 1914. Courvoisier³ reported 131 cases in 1890. According to Wagner the condition is commonest in women and occurs most frequently between the ages of 50 and 70 years. In Wagner's series there were 191 women to 71 men. Skemp and Travnick⁴ reviewed the question in 1936.

It is interesting to note the size of stones which have been removed. Rankin and McKeithen⁵ report one stone 6.9 by 8.5 cm. Burnett⁶ reported a stone 14 cm. in circumference, weighing 636 grains. Clement⁷ a stone 6.3 by 3.1 cm. Coldrey's⁸ patient passed a stone 2 inches by 1 inch by rectum after one week of severe symptoms, followed by recovery. Chiodin⁹ writes of a case where a gall stone was expelled through a vesico-colonic fistula.

The symptoms are usually acute—a severe, persistent colic, followed by pain and vomiting. The colic may be generalized, later becoming localized to one part of the abdomen, but not to a definite point. Peristalsis may be visible. The vomitus contains bile at first, later becoming faecal. For the first few days the patient's condition remains good, then rapidly becomes poor. Diagnosis before operation is rare, and the prognosis depends upon the time of intervention. If operation is performed early the prognosis is good, but the mortality rate is high, due to the lateness at which operation is decided upon.¹ All authorities agree that removal of the obstructing stone is advisable. Because vomiting is usually faecal before intervention, gastric lavage before operation, followed by constant post-operative siphonage, is advised.

The following case report may be of interest.

Mrs. E.S., aged 44, well built, somewhat overweight; blood pressure 160/80.

Past history.—She had complained of "stomach upsets", occurring two or three times a year for the

past five years. No definite diagnosis of her complaints had been made. Some years ago she had been told that her heart was "not strong enough to stand an operation". In October, 1936, she had an attack of "indigestion", at which time I examined her. On examination the chest was clear, the heart not enlarged, though a mitral murmur was heard at times. This murmur was not constant and was not heard one week later. There was slight yellowing of the conjunctiva. Her abdomen was tender to palpation over the gall-bladder region. The urine showed a trace of albumin, but no bile pigment was demonstrated. The stools were dark-coloured. The patient vomited bile-stained mucus. The vomiting was difficult to control but was stopped after 24 hours. A diagnosis of cholecystitis was suggested and x-ray studies of the gall bladder advised. The attack ceased in ten days, and although the patient was reminded on several occasions she neglected to have the x-ray studies made.

On March 3, 1937, the patient complained of pain localized over the lower abdomen. This pain continued and the following day she took phenolax as a laxative. The pain increased and vomiting commenced. The vomitus was bile-stained. She was seen on March 5th. The pain was localized to the lower abdomen. There was no spasm; no peristalsis could be seen; and there was no point of tenderness on deep pressure. The bowels had moved since taking the phenolax. Because of the location of the intestinal pain and absence of other symptoms a diagnosis of intestinal infection was made and treatment outlined. The following day (March 6th) the vomiting increased and a faecal odour appeared in the vomitus. This was not reported until 6.00 p.m., at which time the patient was visited. Intestinal obstruction was diagnosed, but the etiology was not suspected. The patient was admitted to hospital and a laparotomy performed at 8.00 p.m.

On opening the abdomen through a right rectus incision the peritoneum was clear; the gall bladder felt small to the touch. No stones or other obstruction in the gall bladder could be felt. On following the small intestine downward from the pylorus an obstruction was felt approximately six feet from the pylorus. The obstructing object felt hard and was about the size of a large walnut. The intestine was clamped above the mass, and an incision made over the mass. The obstructing material was removed, appearing to be a stone. The intestinal opening was closed. No further investigation was made owing to the condition of the patient.

For the succeeding 24 hours convalescence was fair. Vomiting ceased, and the patient took some fluid by mouth. Since the vomiting had ceased, gastric siphonage was not instituted. About 7.00 p.m. on the following day the patient's condition became suddenly worse. Vomiting had re-commenced; bronchial râles were heard at the base of the right lung; the apex beat was displaced slightly to the left. Although continuous gastric siphonage was started, the patient's condition became progressively worse, and she died at 2.00 a.m., March 8th.

Post-mortem examination by Dr. A. Y. McNair showed the following. The body was that of an obese, well developed and nourished adult white female of apparent age 50.

On opening the abdomen several coils of small intestine were found adherent with fibrinous plastic exudate. There was no general peritonitis and no excess of free fluid. The appendix was healthy. The jejunum had been opened approximately six feet from the pylorus and had been closed layer on layer. Its lumen was

patent. There was no obstruction, nor was any obstruction found in any part of the intestinal tract. The right upper quadrant showed massive adhesions between the transverse colon and the gall-bladder fissure. The duodenum and pylorus were pulled up under the liver and firmly adherent to the gall bladder. There was no perforation into the peritoneal cavity, and no palpable stones were found in this region.

Thorax.—The right pleural cavity was completely obliterated by old dense fibrous adhesions. The left lung was free, showed moderate œdema and congestion, with some focal broncho-pneumonia in the left lower lobe. The right lung showed patchy pneumonia in the right lower lobe. The heart was not increased in size; aorta atheromatous. The coronary vessels were patent throughout, but showed patchy, fairly well marked atheroma. The heart muscle was softened, mottled in colour, with a bluish red tinge. The hilar glands were not enlarged, and there was no mediastinal enlargement or tumour formation.

The stomach was somewhat enlarged and contained 1½ pints of semi-digested food; pylorus healthy. One and one-half inches beyond the pylorus the gall bladder was firmly adherent to the wall of the duodenum and had ulcerated into it, producing a duodenal-gall bladder fistula, measuring 1¼ inches in diameter. The gall bladder was approximately three inches long. Its wall was thickened and very fibrotic. The lumen of the gall bladder appeared to be lined by a greyish slough. Through the opening into the duodenum three stones had passed. The largest was approximately 4 cm. in length and 3 cm. in diameter. The stone was rounded at one end and faceted on the other. This stone had apparently passed down the small bowel and completely obstructed the jejunum at the point where the intestine

had been opened and the stone removed. Two other stones, faceted to match each other and the larger stone, were found in the transverse colon. These two had passed through the ileocaecal valve. Section of the liver at the base of the gall bladder showed it to be much sclerosed, firm, with chronic cholangitis and hepatitis throughout this area. This extended through the liver substance for approximately one and one-quarter inches. This was a long standing cholecystitis with cholelithiasis. The common bile duct was somewhat thickened and the lymph glands all along the common duct were enlarged and easily palpable. The pancreas appeared normal. The uterus, tubes, and ovaries were healthy. The kidneys showed nothing remarkable. The suprarenals were normal.

Anatomical diagnosis.—Choledochoduodenostomy, 1½ inches from the pylorus; intestinal obstruction from gall stones; chronic degenerative myocarditis; terminal hypostatic pneumonia. Microscopic examination confirmed the anatomical diagnosis.

REFERENCES

1. Discussion on acute intestinal obstruction, *Brit. M. J.*, 1925, 2: 993.
2. WAGNER, A.: Ileus durch Gallensteine, *Deutsche Zeitschr. f. Chir.*, 1914, 130: 353.
3. COURVOISIER, L. G.: Beitr. zur. Path. und Chir. der Gallenwege, Leipzig, 1890, p. 101.
4. SKEMP, A. A. AND TRAVNICK, F. G.: Gallstone obstruction of bowel, *Am. J. Surg.*, 1936, 32: 166.
5. RANKIN, F. W. AND MCKEITHEN, A. M.: Gallstone ileus, *Kentucky M. J.*, 1924, 22: 236.
6. BURNETT, C.: Obstruction of small intestine by gallstones, *Brit. M. J.*, 1926, 1: 565.
7. CLEMENT, G. H.: Intestinal obstruction due to gallstone, *Canad. M. Ass. J.*, 1921, 11: 262.
8. COLDREY, R. S.: Intestinal obstruction by gallstone, *Brit. M. J.*, 1926, 1: 783.
9. CHODIN, L. A.: Gallstones expelled through vesicocolonic fistula, *Rev. Med. de Rosaio*, 1935, 25: 759.

CONGENITAL ATRESIA AND VOLVULUS OF THE INTESTINE

(WITH REPORT OF A CASE)

By C. H. AUSTIN WALTERS, M.D.

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CONGENITAL atresia of the intestines is a fairly rare embryonic mishap, although references to it in the literature are relatively frequent. Barring the incidence in the pylorus, rectum and anal canal, it occurs about once in 20,000 births. Theremin¹ however managed to find 9 cases in 150,000 children. It is most commonly associated with imperforate anus (Spriggs²). In 1922 Davis and Poynter³ collected a series of 392 cases, and their report fairly well illustrates the usual sites—duodenum 134 cases, jejunum 60, ileum and cæcum 101, and colon 39. Sixty-seven cases had multiple sites for the deformity. Only 15 per cent of all types of intestinal atresia are multiple however.

There are three main types of intestinal obstruction in this condition: first, that caused by peritoneal bands where the obstruction is only partial, and the child may grow to maturity before there is any trouble; this type occurs

most often in the ileo-cæcal region; second, that caused by a diaphragm or septum lined with mucous membrane, and occluding the intestinal lumen; third, where there is a complete atresia, which means that the bowel ends in a cul-de-sac followed by a collapsed or obliterated gut. Very occasionally there may be gaps in the bowel continuity for short distances caused by multiple atresias, the intervening areas being represented by cord-like or hypoplastic gut. These connecting strands may contain all four layers of the intestinal wall, which may be fused and very difficult to recognize, or even be entirely replaced by fibrous tissue.

There are many theories concerning the etiology of this condition. The most common is that concerning the development of the epithelial buds. Until the fifth week of intrauterine life the alimentary tract is a straight tube without a lumen, but shortly after becomes curved and presents a well defined round lumen lined with epithelium. Soon after, the epithelial buds rapidly proliferate, according to Ladd,⁴ and the lumen becomes

obliterated. This solid stage persists for a short time until vacuoles appear and coalesce, to re-establish a permanent intestinal lumen. If the epithelial buds show an excessive hyperplasia no vacuoles appear and an atresia is present. Another common theory is the inflammatory one. Some claim that the adhesions and bands form as the result of fetal peritonitis, enteritis with ulceration of the mucosa followed by cicatrization of the gut, and fetal arteriosclerosis involving the mesenteric arteries. Still a third theory may be classified as "developmental accidents".⁵ Under this heading may be grouped the following: congenital volvulus and intussusception; traction on a loop of intestine by the omphalomesenteric duct (vitelline duct which serves as a line of communication between the alimentary tract and the yolk-sac early in embryonic life, but usually becomes obliterated during the third and fourth month of intrauterine life) dragging a portion of the intestine into the umbilicus.

The symptomatology is that of any intestinal obstruction, the severity and the time of onset, of course, depending on the site and type of atresia. Briefly the symptoms are: (1) frequent and persistent vomiting; (2) diminution or absence of the stools; (3) absence of bile in the stools; (4) visible peristalsis; (5) dehydration (rapid when the atresia is complete).

The differential diagnosis is sometimes difficult, particularly from pyloric stenosis, where the atresia is incomplete and symptoms are delayed in appearance. Esophageal stricture and imperforate anus are easily ruled out. Volvulus, intussusception, appendicitis, diverticulitis, and strangulated hernia must be eliminated. Barium by mouth or rectum will clinch the diagnosis, but if the atresia is a complete one the use of barium by rectum is certainly contraindicated, since it will block the small lumen of the gut below the attempted operation site. The prognosis at the very best is poor, the jejunum and ileum providing the worst cases.

Surgical interference should be prompt and the block relieved by the simplest means possible. Webb and Wagensteen⁶ found 9 infants successfully operated on out of 500 cases. They also reported that all patients treated by enterostomy died, and they recommended either side-to-side anastomosis or a duodenojejunosomy. Of course, the chances of success in the presence of multiple atresias or a hypoplastic gut, as in the case reported here, are nil. Sweet and Robertson⁷ report in some detail 3 cases and one of their own which were successfully operated on. "The first case in which operation was performed successfully was reported by Fockens, who made an anastomosis between the segments. The second successful case was reported by Ernst, who brought the ileum up anterior to

the colon and anastomosed it to the duodenum. The third case is Richter's, of Chicago, who performed a posterior gastro-enterostomy." Their own case was a complete duodenal atresia. The first operation was an anterior gastro-jejunosomy, and twenty-three days later a second operation was done, since the infant still vomited daily and was losing weight. The anterior aspect of the second part of the duodenum was joined to the jejunal loop distal to the first anastomosis.

The infant is always dehydrated, so that blood transfusion is a necessary procedure. Local is the anæsthetic of choice, ether being only used when absolutely necessary. Shaw⁵ recommends gentle distension of the distal segment of the bowel with warm normal saline, and rightly points out that the successful operation depends upon the ability of the distal segment to take up peristalsis after the obstructed area has been circumvented by an anastomosis.

Intestinal volvulus usually means that a more or less limited segment of bowel has its extremities occluded by the compression of a twisting process, so that its blood supply is seriously embarrassed or completely interrupted by compression of its mesentery. In order to understand congenital volvulus a more comprehensive review of embryology is needed than for the study of congenital atresia. Since the evolution of the midgut of the embryo is quite a complicated growth process, the greater frequency of error in intestinal development is easily understood. Norman M. Dott⁸ gives an excellent description of the embryological growth of the intestines, and the majority of the following facts are taken from his article.

The first evidence of an alimentary canal is the entodermic vesicle of the zygote which by constriction divides into two parts—an intra-embryonic portion which is the future gastro-intestinal tract, and an extra-embryonic portion which is the yolk-sac. The alimentary canal has three main subdivisions—fore-, mid-, and hind-gut. All these are suspended by the common dorsal mesentery. As early as the fourth week the foregut, consisting of stomach, duodenum and a rudimentary pancreas, shows a fixed point where it joins the midgut, due to thickening and shortening of the mesentery. From the upper end of the hindgut, a mesenchymal thickening in the mesentery passes upward to around the origin of the superior mesenteric artery. This band does not keep pace in growth with the midgut or its mesentery, so that it also forms a point of anchorage, which is called the colic angle or flexure. Hence, early in embryonic life, the attachments of the fore- and hind-gut are permanently fixed points, with the midgut swinging as it were between them in a narrow isthmus called the duodeno-colic isthmus.

The midgut grows too rapidly to be entirely accommodated in its original site, so that it is pushed into the root of the umbilical cord about the fourth week as a temporary and physiological hernia. With it goes its mesentery which contains in its folds the superior mesenteric artery. This artery sends branches forward to the anterior segment of the midgut which is called the pre-arterial loop and back to the posterior segment or post-arterial loop. Thus, at the end of the fifth week the midgut consists of a loop of bowel projecting into the umbilical cord, and with the root of the rudimentary appendix and cæcum appearing on the post-arterial loop. The basal attachment of the pre-arterial loop is slightly to the right of the midline. This loop grows more rapidly in length forming a mass of S-shaped loops, (the jejunum). In this manner the superior mesenteric artery tends to become more closely approximated to the post-arterial loop. About the tenth week the midgut begins to return to the abdominal cavity. It is not possible for the herniated gut to return *en masse*, and it is believed that the pre-arterial loop is reduced first, since the larger cæcum, appendix and colon offer more resistance due to their size. The small intestine enters the abdomen on the right side of the superior mesenteric artery, and, as its coils collect it is pushed into the available space behind the artery by the coils of the following post-arterial loop. These coils (pre-arterial) push upwards on the hindgut, displacing it further up, making the splenic flexure of the colon. The last part of the cæcum and ileum carries the terminal part of the superior mesenteric artery with it as it enters the abdomen, and the cæcum then lies free in the region of the umbilicus on a plane anterior to the small intestine and the artery. The colon, tending to straighten out, carries the cæcum and appendix upwards and to the right underlying the liver, and the colon comes to lie across the pedicle of the intestinal mass at the origin of the superior mesenteric artery. Following this, the colon then begins to elongate, and the cæcum is pushed downwards into the right iliac fossa to its usual position. This entire rotation of the midgut when it is returning from the umbilical cord to the abdominal cavity is an anti-clockwise turning about the axis of the superior mesenteric artery. Thus the duodenum crosses *posteriorly* to the artery at its origin, while the colon crosses at the same point *anteriorly*.

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ring the duodenum gradually dilated from its ordinary size, and 50 cm. from the pylorus the jejunum ended in a greatly distended, early gangrenous, completely closed cul-de-sac measuring 15 cm. in diameter. The mesentery, however, was complete, and bridged a gap of 1.25 cm. from the cul-de-sac to where the jejunum began again, now a thick, cord-like tube. On tracing the gut along other points of atresia were found. A normal appendix was present (almost as large as the ileum itself), but the caecum and entire colon down to, and including, the recto-sigmoid did not vary in size or appearance from the hypoplastic jejunum or ileum just distal to the atresia. Except for the slight angulation and the presence of the appendix at the ileocaecal junction, it would have been almost impossible to distinguish large from small intestine. On opening this undeveloped gut the lumen was found to be very small, and the finest probe could only be passed along it with difficulty. The lumen contained streaks of viscid cord-like mucus. The absence of bile in this portion of the intestine would indicate that the obstruction probably occurred before the third or fourth month of embryo life, since the biliary secretion first makes its appearance about the sixteenth week. The anus was not imperforate, and the lumen of the rectal portion of the gut was more developed than that in the recto-sigmoid and above it. This accounted for the infant being able to take about half an ounce of the enema. No other congenital abnormalities were present in any of the other abdominal organs.

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REFERENCES

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ABDOMINAL PREGNANCY COMPLICATED BY APPENDICITIS
AND BILATERAL PYOSALPINX*

BY W. F. PLEWES

Toronto

THE literature pertaining to abdominal pregnancy is most interesting. Cases were reported as far back as 1809, and from almost every country. Two have been reported from Canada.

Hellman and Simon,¹ New York, collected 316 cases of abdominal pregnancy which had been reported from 1809 to 1935. One hundred and fifty-eight of these lived eight days or more. Of 316 mothers, 212 lived, 101 died, and in 3 the result is not known. In this series there were only 80 cases in which mother and child both survived. There were 2 cases of combined intra-abdominal and intra-uterine pregnancy—all lived. There were 4 cases at full term. One case reported from Norway was retroperitoneal. Posner,² New York, reported a living child at term, the mother of which died. Voegelin,³ of Philadelphia, removed an abdominal lithopædion which had been dead 18 years. Sarkar,⁴ of Calcutta, removed a 28-weeks old fetus which had been dead six months; the mother lived. In Brussels, a 7½ month dead fetus was removed; the sac contained pus; this mother died. Bonfield,⁵ of Ottawa, in September, 1935, removed a 5 months' retroperitoneal dead fetus. Eisaman and Ziegler,⁶ of Pittsburgh reported a living child at term. In a series of 28,000 pregnancies 3 were reported as abdominal.

The complications were: eclampsia; twins; abdominal pregnancy and tubal pregnancy; abdominal pregnancy and tubal lithopædion; abdominal pregnancy and fibroma. The principal causes of death in this series were (in this order) peritonitis, hæmorrhage and shock, diseases of the heart and kidney, pneumonia.

Another series is reported by Cornell and Lash.⁷ In 86 cases in which the baby was born after the sixth month the infant mortality was 22 per cent. In 60 cases in which the baby was born alive in the eighth or ninth month the infant mortality was 35 per cent. The maternal mortality was 14.3 per cent (34 cases).

In 236 cases at the Cook County Hospital peritonitis and shock caused 25 of the 34 deaths.

Schumann reports a case in which an ovum with a sac of one inch diameter had become so firmly imbedded upon two neighbouring coils of the ileum as to produce intestinal obstruction.

Reel and Lewis⁸ report 10 cases of abdominal pregnancy. The incidence of the latter in this series is 0.28 per cent of all pregnant women admitted during seven years and 3,437 cases. A common factor in this series was a relatively long period of sterility preceding the abdominal pregnancy. Two women had not been pregnant for 12 years, 1 for 10, 4 for 9, and 1 for 3; 1 was multiparous.

The diagnosis of abdominal pregnancy is, to say the least, complicated and difficult. Even brilliant surgeons such as Berkley, Bonney, Kelly, and Cullen state unashamed that they

each have made mistakes in the diagnosis of this condition. E. B. Woods,⁹ in his series of 236 cases, states that only 35 per cent were diagnosed correctly before operation. In any case of suspected pregnancy it is usual to apply the Aschheim-Zondek test, but should the fetus not be alive and the placenta cease to function one would not expect the test to be positive. It is not always possible to be sure that the examining finger can separate the body of the uterus from the main tumour, especially should the placenta be situated in the pouch of Douglas. More than one author states that discoloration of the umbilicus is diagnostic of internal hæmorrhage.

A few words here in regard to the disposal of the placenta would not be out of place as most authorities mention it at length. E. P. Davis¹⁰ states: "The effort to separate the placenta is attended with great risk of fatal hæmorrhage". Delay has been advised by some to allow the fetus to die and the placenta to become partly separated. When the fetus has been removed and the placenta found to be firmly attached to the bowel, it is suggested that the membranes be stitched to the abdominal wall and the placenta allowed to remain while the amniotic sac is packed with sterile gauze. The pressure preventing hæmorrhage, the placenta becomes gradually loosened, sometimes piecemeal and sometimes almost entirely.

Reel and Lewis in their report state that there are two ways to treat the placenta: (1) marsupialization, *i.e.*, packing the cavity and allowing the placenta to slough; (2) if no infection be present, to divide the cord and leave the placenta to be removed by absorption. In these ten cases cul-de-sac drainage, consisting of plain gauze packing, was used in 3, while in 7 abdominal drainage was maintained. The mortality of this series was 20 per cent (2 cases). One died from complete bowel obstruction. The other could have been saved by transfusion but they failed to secure a donor in time.

E. B. Woods states that the maternal mortality can be lowered by leaving the placenta.

* Read before the Section of Obstetrics and Gynecology, Academy of Medicine, Toronto, January 13, 1937.

Bonney states that in the absence of pus he leaves the placenta where it is attached to the bowel, claiming that the danger of post-operative hæmorrhage is too great and that the sterile placenta does no harm if left. Beck¹¹ also agrees that if the placenta is firmly attached to the bowel it should be left *in situ*, since the usual mechanism for the control of hæmorrhage from the placental site is absent. If infected, marsupialization is recommended. If hæmorrhage from a partly separated placenta occurs the sac is sutured to the margins of the abdominal wall and packed with gauze.

CASE REPORT

Mrs. B., aged 31, was admitted to the Toronto East General Hospital on July 7, 1936. She had been married 14 years; one pregnancy 13 years ago. She complained of a bearing-down sensation and aching pain in the lower abdomen for five months, irregular bleeding for four months, sometimes dark but usually bright red, and frequency of micturition during the first two months of her illness. During this time she became increasingly aware of a dull ache in the right lower quadrant.

On admission: temperature, 101° F.; pulse, 96; respiration, 22; red blood cells, 4,600,000; hgb., 75 per cent; white blood cells, 26,200. The temperature reached 103° F. daily, and the leukocytes dropped to 15,000 in four days. The Aschheim-Zondek test was negative. Urine: acid, no sugar, no albumin. Both urethral and cervical smears showed pus cells, an occasional pair of Gram-negative cocci, but no intracellular organisms.

On physical examination, the abdomen presented an irregular enlargement resembling three tumours. The most prominent was on the right side and extended from below upward above the level of the umbilicus. The left-sided tumour was next in size, and the middle one extended to just below the umbilicus, and was the smallest mass. These were all very tender and firm, as firm as fibroids. (Multiple fibroids undergoing degeneration were seriously considered in the differential diagnosis). Bimanual examination revealed a large, soft, patulous cervix. Both fornices were very tender. There was a semi-solid or cystic mass in the pouch of Douglas which later proved to be placenta. The uterus could not be outlined at this time, as separate from the masses described above.

Operation.—Laparotomy on July 22nd. On opening the abdomen the omentum was found markedly congested and firmly adherent to a large irregular mass which reached as high as the umbilicus in the mid-line, on the right some two inches higher, and on the left two inches lower. The cæcum was adherent to a large right Fallopian tube which formed a mass 1½ inches in diameter and 6 inches in length. The descending colon was adherent to the left tube which was nearly as large. The great omentum was dissected from the mass and the appendix was seen to be distended with pus, gangrenous, and deeply imbedded in the right tubal mass, extending to the left of the mid-line. In separating the cæcum from the right tube an opening was made into an abscess cavity from which 600 c.c. of greyish non-odorous pus was aspirated. This decreased the size of the mass generally, and it was found that the central part of the tumour was covered by a thin membrane. When opened, this revealed a fetus of about four months. There was an extra long cord. The placenta was almost detached, only a small edge of it being adherent to the rectum. Both tubes and appendix were removed as well as the placenta. There were several intramural fibroids in the small uterus, so a subtotal hysterectomy was performed. The wound was closed in layers around two drainage tubes. The wound discharged for 45 days, but otherwise recovery was uneventful. The patient left hospital on September 11th.

The bacteriological report of the pus from the pelvic abscess was "diphtheroid bacilli, probably non-pathogenic".

REFERENCES

1. HELLMAN, A. M. AND SIMON, H. J.: Full term intra-abdominal pregnancy, *Am. J. Surg.*, 1935, 29: 403.
2. POSNER, A. C.: Abdominal pregnancy, *Am. J. Obst. & Gyn.*, 1935, 30: 293.
3. VOEGELIN, A. W.: Abdominal pregnancy with removal after 18 years of 6 months lithopedion, *Am. J. Obst. & Gyn.*, 1935, 30: 129.
4. SARKAR, A.: Case of advanced abdominal pregnancy, *J. Obst. & Gyn. Brit. Emp.*, 1935, 42: 1122.
5. BONFIELD, J. P.: Case of extrauterine pregnancy, *Canad. M. Ass. J.*, 1935, 33: 308.
6. EISAMAN, J. R. AND ZIEGLER, C. E.: Abdominal pregnancy, *J. Am. M. Ass.*, 1935, 104: 2175.
7. CORNELL, E. L. AND LASH, A. F.: Report of 10 cases of abdominal pregnancy, *Illinois M. J.*, 1934, 65: 462.
8. REEL, P. J. AND LEWIS, T. F.: Secondary abdominal pregnancy, report of 10 cases, *Am. J. Obst. & Gyn.*, 1936, 31: 957.
9. WOODS, E. B.: Abdominal pregnancy at term with delivery of normal living child, *Am. J. Obst. & Gyn.*, 1936, 32: 155.
10. DAVIS, E. P.: A Treatise on Obstetrics, 2nd ed., Lea & Febiger, Phila., 1904, p. 279.
11. BECK, A. C.: Obstetrical practice, Williams & Wilkins, Baltimore, 1935, p. 413.

CLIMATE AND RHEUMATIC HEART DISEASE: SURVEY AMONG AMERICAN INDIAN SCHOOL CHILDREN IN NORTHERN AND SOUTHERN LOCALITIES.—For measuring the geographic prevalence of rheumatic heart disease J. R. Paul and G. L. Dixon determined the rates (or percentage) of such cases as could be found among three groups of Indian school children in northwestern and southwestern sections of this country. The choice of these Indian populations has rested on the fact that there is a general similarity from the standpoint of race among some North American Indian tribes which is not found among other groups of Americans, and also that, regardless of their geographic locality, there is a general similarity of their living conditions. Their illnesses, therefore, should be truly representative of local, living and climatic conditions. In the cold though relatively

dry climate of Wyoming and Montana the prevalence of rheumatic heart disease (4.5 per cent) is high, in comparison with rates determined in New England (2.2 per cent), whereas in the warm though dry climate of southern Arizona it is correspondingly low (0.5 per cent). In other words, rheumatic heart disease is almost ten times as frequent among western Indians living in regions close to the Canadian border as it is among similar groups living close to the Mexican border. It is probable that the clinical course of rheumatic fever in the southwest may be milder than that usually encountered in the north, but no evidence was found in this survey suggesting that the apparent mildness of the clinical picture of rheumatic fever in the southwest may allow rheumatic heart disease to develop with an unsuspected frequency comparable to that seen in more northern climates.—*J. Am. M. Ass.*, 1937, 108: 2096.

Case Reports

A CASE OF STREPTOCOCCUS SEPTICÆMIA

By W. S. HODGINS, M.D.

Windsor, Ont.

Mrs. McC., aged 20 years, was admitted to Grace Hospital on Saturday, April 17, 1937. Before her admission to the hospital her temperature was 106° F., and upon admission it registered 105.2° F. A blood culture was taken which was positive for streptococcus. She was immediately put on 5 c.c. prontasil every three hours for five days, and the temperature remained between 104 and 105° F. On the fifth day the prontasil was doubled to 10 c.c. every four hours, with prontylin grains 10 every six hours. The preparations used were those of the Winthrop Chemical Co. of Windsor, who were the first in Canada to manufacture them. The following morning the temperature dropped from 105 to 101° F., rising again in the evening to 102° F. On the morning of the 23rd the temperature had dropped to 99° F., when another blood culture was taken which still showed a positive streptococcus. From the 24th on the temperature remained between 97 and 98° F., on which date a blood transfusion of 300 c.c. was given. The red blood cells were 3,000,000; on 24th had dropped to 2,610,000. On the 25th another blood culture was taken which was negative for streptococcus. On the morning of April 30th, another blood culture was taken, which still showed a negative culture streptococcus. The prontasil was discontinued on the 25th and the prontylin continued, 10 grs. every six hours, until the 27th. The patient was discharged on May 1st, and continues to make wonderful progress. She is now receiving treatment for her anæmia.

This is an outstanding case and shows the wonderful effect of prontasil and prontylin. I feel quite certain that we are now able to control streptococcus infection of almost any severity if we push this preparation to maximum doses.

EARLY RUPTURE OF ECTOPIC PREGNANCY

By S. A. WALLACE

Kamloops, B.C.

Ectopic pregnancies rupturing as early as seven days after conception have been reported. In the case reported here rupture occurred apparently nine days after. When such ruptures can occur so early it is evident that one must keep the possibility in mind.

Mrs. McG., aged 22, finished a regular and normal menstruation on November 29, 1936. Previous menstruations had been quite regular, and this last occurred on the proper day and lasted the usual length of time. On December 8, 1936, in the early morning she was taken with severe pain in the right lower quadrant, vomited, and felt quite weak. The pain was irregular and subsided a little during the day, but did not go away entirely. About this time she began to flow again rather heavily. The pain continued and as time went on spread across the midline to the lower left quadrant. She was seen on December 13th, after an eighty-mile

drive from the Vidette Mine over rough roads. She looked quite pale and was rather tender in the region of the right tube. Bimanual examination showed a normal uterus. One could not be sure of a mass, although there was more tenderness in the right fornix. Diagnosis of ectopic pregnancy was made, and a laparotomy was performed on December 14th. The lower part of the peritoneal cavity was filled with old blood clots. The uterus was not enlarged. The right tube in its distal third was distended to the size of one's forefinger. From the fimbriated end a dark clot was protruding. The right tube was removed and the blood clot evacuated. I was rather surprised to find the appendix quite tense and congested, with a concretion in its distal portion and a constriction proximal to this. The appendix was also removed. The patient made an uneventful recovery and left the hospital ten days after operation.

PIGMENTATION OF AMNIOTIC FLUID, SAC, AND VERNIX CASEOSA, AND BANDL-LIKE RING OF UTERUS

By J. E. McARTHUR, B.A., M.D., C.M.

Noranda, P.Q.

To my mind this is an unusual and interesting case.

An obstetrical patient, a Hebrew woman, aged 26 years, a multipara, with her second baby, at full term, went into labour on August 30, 1936. After having had grumbling pains for about three hours from 3 p.m., I saw her and had her admitted to hospital. The baby was in a left occipito-anterior position. As her pains became more severe she was given in all 3 grains of nembutal and gr. 1/12 (H) heroin hydrochloride. About 10.30 the same night she was delivered of a healthy-looking and well developed baby boy weighing 7 pounds, 10 ounces. Delivery was quite short and easy, and no forceps used. Light chloroform anæsthesia was administered. The amniotic fluid instead of being clear in colour was very distinctly yellow. The amniotic sac, the fetal covering of the placenta, and even the maternal side of the placenta, but to a lesser degree, the cord, and the vernix caseosa were also very bright yellow in colour. The amniotic fluid was not excessive in amount and was of about the normal specific gravity. The baby itself, strangely enough, apart from the vernix caseosa, did not share in this pigmented condition. The meconium and urine, as afterwards observed, showed no abnormal pigmentation. The baby's skin was of a healthy pinkish colour. The mucous membranes were also pinkish red in appearance. There was no icteroid tinge to the conjunctivæ. Neither did icterus neonatorum develop afterwards.

After waiting an hour for the placenta to come away, having catheterized the urinary bladder, and after using the ordinary methods of coaxing the placenta out, a Credé was done and then a Credé under an anæsthetic. In spite of these efforts I was only able to express about a quarter of the lower end of the placenta. This part presented according to the Duncan method. It was then felt that the upper part of the placenta must be firmly held to the posterior wall, so I scrubbed up again, put on a new pair of sterile gloves, and with the patient deeply anæsthetized, I proceeded to do a manual removal. I was able to put my whole hand into the lower uterine

segment and follow upward the placenta which was attached to the posterior wall of the uterus. Trying to enucleate the upper pole of the placenta I came upon a constriction about the middle of the uterus through which I could only pass my index and middle fingers. Above and below this ring the uterus could be felt by bi-manual examination to be hour-glass-like, in the superior cavity of which the upper half of the placenta was firmly attached to the posterior wall of the uterus. The placenta was then disengaged from the wall and removed only with some difficulty through the yet tight contraction ring. On examination of the placenta which came away *in toto* there was a very marked constriction about its middle, which corresponded to the contraction ring in the uterus. Apart from this and the pigmentation above described the organ was normal.

In the whole third stage the patient lost only about 250 c.c. of blood. When the placenta was removed the uterus contracted down so that if there was any contraction ring left it could not be felt on abdominal palpation. The mother made an uneventful recovery and showed no signs of post-partum infection. The baby also ran a normal course.

The mother's ante-natal history and physical examination were negative except for a few points on which I should briefly comment. She was a woman of small frame, weighing before pregnancy 90 pounds. Her external conjugate was between 17.5 cm. and 18 cm. Her complexion was sallow and characteristic of her race. Her conjunctivæ showed no icteroid tinge. Her blood pressure and urine were always within normal limits. Her blood Wassermann test was negative. During her pregnancy she enjoyed fairly good health except for slight attacks of nausea during the first three months and "indigestion" relieved by taking alkalis. Her first baby, one and a half years before, was a forceps' case. At that time, I am ashamed to say, she bled rather excessively after the placenta came away.

This bleeding at the time I attributed to atony of the uterus, but afterwards I learned it was due to a retained placenta succenturiata which I failed to recognize at the time of delivery, and which, two weeks afterwards, under general anæsthesia, I removed digitally.

SUMMARY

In reviewing the ante-natal examination of the mother, the therapeutics used, her dietary regimen, her post-partum course, and the absence of any suggestive findings in the baby, I am at a loss to explain this abnormal pigmentation. Unfortunately, because of the lack of the necessary facilities, no biochemical, or pathological examination of the amniotic fluid and placenta was made. Whether or not the cause of the pigmentation was related in any way with the Bandl-like ring of the uterus preventing delivery of the placenta I do not know. Furthermore, is it possible that this woman had had a contraction ring of the uterus at the time of the delivery of her first baby, and that this prevented the evacuation of the part of placenta which later had to be removed?

REFERENCES

1. WILLIAMS, J. W.: *Obstetrics*, 7th ed., Appleton-Century, N.Y., 1936, p. 175.
2. FABRE AND CONVERT: A case of retention of the placenta due to contracture of Bandl's ring, *Bull. Soc. d'Obs. de Paris*, 1911, 14: 53.

Editorial

THE OTTAWA MEETING

THE Annual Meeting of our Association, held this year in Ottawa from June 21st to 25th, has passed into history. Our recollections of it are of the pleasantest. Ottawa, as the capital city, has special attractions and full use was made of them. The work of the local committees, so arduous at all times, bore abundant fruit. The program was well arranged and there was no clashing between general and special sessions. A feature specially worthy of comment is that the discussion of the principal papers had been arranged beforehand, thus ensuring against loss of time and more or less desultory talk. If we remember rightly, this plan was adopted at the meeting in Ottawa fourteen years ago, though in the interval it has fallen largely into desuetude. Worthy of praise, too, is the printing in the official program of short abstracts of the papers, thus enabling the members to select

in advance those subjects which they desired to hear about. The scientific program did not present any startling discoveries; it seldom does; but many of the papers presented were of solid excellence, and certain of the leaders in the profession, in Canada, Great Britain, the United States, and France took part. Perhaps the high spots were the presentations of Prof. Antoine Lacassagne, of Paris, on "The Relation between Hormones and Cancer"; of Sir Beckwith Whitehouse, of Birmingham, on "Salpingitis", and of Mr. Watson Jones, of Liverpool, on "Modern Developments of Fracture Treatment", and "The Treatment of Bone and Joint Infections", which attracted large audiences. The position of Blackader Lecturer was worthily held by Dr. H. B. Cushing, who took as his text "Rheumatic Fever and Heart Disease in Childhood."

Several matters of prime importance occupied the attention of Council. Dr. Routley, the General Secretary, reported on his recent visit to Great Britain and the Continent, where he went to acquire first-hand knowledge in regard to health insurance schemes. His report will, doubtless, appear in print in due course. It was reported that the Board of Trustees of The King George V Silver Jubilee Cancer Fund had allotted the sum of \$14,000 annually, being the income from the Fund, to the Canadian Medical Association, to inaugurate the fight against cancer. This recognition of our Association as the body best equipped to undertake this task is most gratifying. The matter is now in the hands of Dr. J. S. McEachern, Chairman of the Cancer Study Committee, and some subcommittees have been struck which are working out the practical details. Federation of the provincial Associations with the national Body is still in the air, but substantial progress is being made. Only a few minor details, brought forward by the Ontario Medical Association, but, apparently, embodying certain difficulties advanced by some of the other provinces, also remain to be adjusted. The principle of the changes suggested has been adopted and the Committee on Constitution and By-laws has been instructed to draw up the necessary changes in the wording of our Constitution. It is confidently expected that federation of all the provinces will become a reality at the annual meeting next year. The chief difficulty at the moment seems to be, in the case of those provinces in which the medical men pay one fee for licence and membership in their provincial Associations, how to arrange for the entrance into the Canadian Medical Association of those who do not desire to pay the necessarily increased fee. But, no doubt, a way out will be found.

The entertainment provided was beyond praise. The Dinner proffered to the Council by the Ottawa Medico-Chirurgical Society was a masterpiece of gastronomic excellence. The Garden Party at the Country Club was delightful. The high spot, of course, was the Annual General Meeting on the Wednesday evening, which was followed by the President's Reception. This was a gala affair, as the Executive and certain of the invited guests wore their academic robes, and many

of the principal citizens of Ottawa, including Church and State, graced the platform. With the beautiful dresses of the ladies the colour note was much in evidence. A pleasing feature of the occasion was the conferring of Honorary Membership in our Association on our distinguished visitors, Sir Beckwith Whitehouse, Professor of Obstetrics and Gynæcology in the University of Birmingham, who brought greetings from the British Medical Association; Mr. R. Watson Jones, orthopaedic surgeon, of Liverpool; Prof. Antoine Lacassagne, of the Radium Institute of Paris; and Dr. John S. Lundy, anæsthetist, of Rochester, Minnesota. Dr. R. E. McKechnie, of Vancouver, a former president, Dr. John Knox McLeod, of Sydney, N.S., and Dr. S. E. Fleming, of Sault Ste. Marie, Ont., were made Senior Members. Much of the success of the gathering was due to His Excellency the Governor-general who graced the proceedings with his presence and received the many guests at the conclusion of the ceremony. His Excellency also gave an admirable address at a luncheon held on the same day in which he praised the work of the medical men, especially those carrying on, under difficulties in the outlying districts. He whimsically suggested that medical scientists might be well employed in devising means to cope with certain insect pests of which he had had experience on some of his recent trips! He held, too, that the doctors were the true life-savers and not the pacifists.

A pleasing innovation was the provision of entertainment for the juniors of whom about 298 were registered. In fact, so attractive was this part of the program that many of the seniors seemed to have renewed their youth, for they also attended in numbers. This feature was so excellent that it probably has come to stay. It will be difficult for any subsequent committee to strike an original note, but it was facetiously suggested by one member that if our Hali-gonian brethren next year hope to outdo the friends from Ottawa they will have to institute a crèche!

Following the precedent established last year by the Ontario Medical Association in setting up a Scientific Exhibit the Ottawa Committee decided to do likewise. The result was an exhibit of about fifty items,

well displayed, and highly informative. The Commercial Exhibit, also deserves praise.

The thanks of the Association are gratefully tendered to His Excellency the Governor-general, His Worship the Mayor of Ottawa, the President, Dr. T. H. Leggett and Mrs. Leggett, the Past-president, Dr. Hermann Robertson and Mrs. Robertson, the President of the Ottawa Medico-Chirurgical Society, Dr. Lorne Gardner, and Mrs. Gardner, and the members of the various committees, both ladies and gentlemen, too numerous to mention, but whose efforts we

appreciate. Those who entertained privately are not forgotten.

The attendance at the Meeting was very satisfactory, rather more than two thousand, men, women, and children, being registered. No doubt this was to a large extent accounted for by the fact that the Ontario Medical Association, on this occasion, joined forces with the National body. A satisfactory feature also was the fact that there was a considerable representation from British Columbia and from the Maritime Provinces.

A.G.N.

THE AUTOMOBILE ACCIDENT FROM THE STANDPOINT OF PREVENTIVE MEDICINE

THIS is the season for highway accidents. One is appalled at the number of fatalities, not to say injuries, that are recorded daily in the press. Or, rather, we would be appalled were it not for the fact that these occurrences are so commonplace that they fail to register with us. Yet, we all have a responsibility, not only to keep ourselves out of trouble, but, as doctors, to point out to others how they may keep themselves out of trouble.

In the matter of road accidents there are four chief factors to be kept in mind—the roadway, the machine, the weather, and the personal equation. The roadway and the machine have for long occupied the attention of the engineers. It is probably correct to say that the automobile is at the present time safer and more dependable than ever; it is as responsive to the touch as a grand piano. Only in one respect can it be criticized; it is capable of too great speed, and excessive speed brings its own dangers. Much of the danger attendant on automobiling is due to the increasing numbers of machines on the road, speeding, and the fact that the roadway in many instances is not adequate for the calls made upon it. Happily, road engineers are fully aware of the situation and roads are being widened, straightened, and graded to meet the present-day demands. The weather, however, is beyond our control. Poor visibility due to fog, rain, or dust, accounts for some accidents, and a slippery roadbed for even more. The careful driver is aware of all this and

will be on his guard. It is of the human element that we wish to speak at the moment.

Granting the importance of the factors already referred to in relation to automobile accidents, we are inclined to think that the human element has not been sufficiently stressed. All the road conditions may be ideal, the machine, perfect, and yet the inadequacy of the human factor may precipitate a catastrophe. It is a commonplace of knowledge that no one should drive an automobile when drunk or asleep. Yet some do. The law takes cognizance of such. It is safe to say that no one should take even a small amount of alcohol shortly before embarking on a drive. Alcohol, taken with a meal, may be slow in action and exerts its effects only after the recipient has been on the road some time. It tends to cause foolhardiness and prolong the latent period. Fatigue, also, tends to vitiate good judgment and delay responsive action. We wonder, too, whether any one has noticed the soporific effect of a steady hum and a straight road. The purring of a perfectly acting engine and the strain of keeping the eyes fixed on a long stretch ahead seem with some to exert a hypnotic influence. This will, of course, be more marked in the case of those who are already fatigued or who are suffering from eye-strain. Much depends on the reserve of energy that the automobilist possesses. Age, sex, rest, and the state of health count in this particular.

Just as we attempt to control disease by the institution of departments of health, by

food inspection, sumptuary laws, and the instruction of the general public, so we may hope to better conditions in automobile traffic by improving our roads, perfecting our machines, inculcating commonsense rules in the minds of the automobiling public, and by drawing attention, as physicians, to certain states of health which render automobiling hazardous.

We all know that, occasionally, drivers of automobiles collapse at the wheel, while their charges career wildly down the street, to the hazard of any who happen to be in the way. Have we to do here with sudden heart failure, with the coma of diabetes or epilepsy, or with cerebral apoplexy? In cases of reckless driving have we to do, sometimes, with a manic-depressive who exhibits his active impulsive phase in this way? We do not know, but we ought to know. Do we know yet how many accidents are attributable to deafness, defective vision, improper eyeglasses, colour-blindness, night-blindness, the so-called "tunnel-vision"? How many to mental abnormalities—psycho-neuroses, relative feeble-mindedness, abnor-

mal outlooks or emotional reactions, paranoia, and the mental disturbances of hyperthyroidism and myxoedema? In short, does it not seem that the prospective driver of an automobile should undergo a thorough test of his physical fitness for his duty before receiving his licence? In only one place do we know that anything like this is being done. In the City of Detroit local judges refer certain violators of traffic rules to the Psychopathic Clinic in the Recorder's Court for a very complete set of tests, including a physical examination, a neurological examination, an intelligence test, a psychiatric examination that includes an appraisal of the culprit's attitudes and emotional states, in addition to determining his knowledge of how to handle a motor. This is all very well, of course, and a great advance, but you will notice that such examinations are only put into operation *after* an accident has taken place and not *before*. Doubtless, however much valuable information will be obtained in this way which will be of guidance towards the next step, which is PREVENTION.

A.G.N.

THE PRESENT POSITION OF THE ONTARIO MEDICAL ASSOCIATION IN RELATION TO MEDICAL ECONOMICS

THE Ontario Medical Association has for many years studied the problem of supplying medical care to large sections of the population by means of what may be broadly termed "Health Insurance". This problem has been approached with an open mind, and the reports of successive Committees on Inter-Relations have presented to the medical profession much valuable information. The studies conducted may be briefly enumerated:—

- (1) A survey of social and economic factors relating to present-day practice.
- (2) An outline and analysis of typical State Medical Service schemes in various countries of the world.
- (3) A questionnaire to the doctors, by which the profession, who replied overwhelmingly, declared their approval of the principle of Health Insurance and gave encouragement to further study, and guarded leadership of the movement.

- (4) An outline of a plan for Health Insurance for the Province of Ontario.
- (5) An intensive study of the 1934 Report on Health Insurance of the Canadian Medical Association's Committee on Economics and recommendations for its revision.
- (6) An introductory study of contract practice.
- (7) A setting forth of the principles of VOLUNTARY Health Insurance for the guidance of affiliated societies or others interested in establishing a local scheme.
- (8) A survey of the available literature on the Cost of Medical Care in Canada, United States, and elsewhere.

In addition to this the Association has had the practical experience of the complete administration of a limited medical care to those persons in receipt of relief in the Province of Ontario for the past two years. The Government turns over to the Ontario

Medical Association the sum of 35c per month for upwards of 400,000 relief recipients, to provide for office and home calls and confinements in the home, together with the necessary drugs and supplies. This service has been carried on to the complete satisfaction of the Government and the patient, and, while the doctors have been paid only a varying percentage of their tariff of fees, the profession has demonstrated its ability to conduct a scheme of this magnitude.

The need for a plan for the provision of a complete medical and hospital service for individuals of limited income has been appreciated by the Ontario Medical Association. In anticipation of the institution of such a plan by governmental agencies the Association has prepared a detailed outline of a service on a compulsory and contributory basis which we believe is adequate and fair to all parties concerned. It has not been the policy of the Association, however, to advocate the institution of compulsory health insurance until public and governmental opinion has indicated that it is desired by the people. When and if such a time arrives the organized medical profession of Ontario is prepared to cooperate with the government, and stands ready to administer the medical services.

Realizing that the actual cost of providing a complete medical and hospital service under the conditions existing in this Province can only be determined by the operation of such a scheme, the Directors and the Council of the Association approved of the request of three branch societies for assistance in the establishment of a plan for the voluntary prepayment for medical services in their respective areas. The Academy of Medicine, Toronto, the Norfolk County Medical Society, and the Essex County Medical Society, representing a large urban, a chiefly rural, and an industrial region, respectively, were the branches interested. The Directors authorized the loan of \$5,000 of Association funds to the Health Insurance Committee to assist in the inauguration of the proposed voluntary plan. An incorporated body known as "The Associated Medical Services Inc.", was set up, with a Board of Directors composed of physicians and laymen, to arrange for the services required in the prevention and treatment of illness on a non-

profit, prepayment, and voluntary basis. This corporation is quite distinct and separate from the O.M.A. but the Association is interested in the success of the venture and expects that valuable information will be gained from this experiment in medical economics.

The Associated Medical Services, with a jurisdiction over the Toronto and Norfolk areas, is about to enrol subscribers and will enlist the cooperation of all legally qualified medical practitioners who agree to practise under the rules of the Corporation. The fees to be charged to subscribers are as follows:—Subscriber, \$2.00 per month; 1st Dependent, \$1.75 per month; 2nd Dependent, \$1.50 per month; 3rd Dependent, \$1.25 per month; 4th and each subsequent dependent, \$1.00 per month.

The benefits to be rendered are:—

- (1) The services of participating physicians in home, office, or hospital, including consultation;
- (2) surgical procedure within the scope of a competent surgeon;
- (3) semi-private available accommodation or a sum not to exceed \$3.50 per day towards the cost of hospitalization in an approved hospital;
- (4) all necessary nursing;
- (5) maternity service to subscribers who have paid dues for 10 consecutive months previous to confinement. There will be a two months' probationary period and the subscriber must pay 3 months' subscription before becoming entitled to any service. Mental illness and chronic tuberculosis in institutions are not included as eligible for treatment.

As previously mentioned, the actual cost of medical care can only be disclosed by the operation of the scheme, and the subscription rates will be adjusted accordingly when this information is available. The plan to be successful must adequately provide for the services rendered, and, as no contributions are forthcoming from others than participants this adjustability is important. It is proposed that payment to doctors shall be on a unit of service at minimum O.M.A. tariff rates. This, while requiring more organization and supervision than payment *per capita*, is believed to be conducive to a better type of service, and will provide much needed statistics.

A. D. KELLY.

Editorial Comments

Tuberculosis in College Students

During the past five years the health of college students has attracted particular attention, and here, notably, and as one would expect, the subject of tuberculosis looms large. This *Journal* has already called attention to the importance of the matter,¹ and has stressed the necessity of diagnosing the condition early, by means of tuberculin-testing and the x-ray, instead of waiting until students come for advice of their own volition. In so far as our short study of the matter is concerned we have found that tuberculosis is not unduly common among the students of Canadian colleges. However, our information is based largely upon impressions and the discovery of pulmonary lesions on routine physical examination. As all know, tuberculosis is an insidious disease and may be far advanced in some cases before symptoms are produced definite enough to induce the student to consult a physician. The story, therefore, might be different, indeed, would be different, were routine tuberculin tests systematically applied to all students, together with x-ray examinations in selected cases. So far as our information goes, only one of our Canadian universities attempts to do this—the University of Saskatchewan. All of them should do it. The opinion of most of those in the United States who are dealing with this matter is definite, that an active program for detecting the disease early is much preferable to a passive one in which the responsibility is left to the student to call for help only when he thinks he needs it. For instance, Diehl,² of the University of Minnesota, stated that among 2,500 students entering in 1931 a program of tuberculin-testing and the x-raying of positive reactors resulted in the finding of fifteen cases of active tuberculosis, of which one was far advanced, five were moderately advanced, and five were minimal. He said, "Had we depended on physical examination and history alone for ordering x-rays of the chest ten of the fifteen cases would have been missed". Also, Stiehm, of the same university, in a study of 2,412 students, found that the institution of a definite case-finding program greatly increased the number of cases of pulmonary tuberculosis discovered—430 per cent above the average for a previous fourteen-year period. What need we of any further witness?

One of the difficulties in obtaining comparable statistics lies in the fact that the investigators of this problem did not use the same

preparation of tuberculin. Now, however, a good many colleges have fallen into line and are using the standardized tuberculin adopted by the Committee on Medical Research of the National Tuberculosis Association, namely, purified protein derivative tuberculin. In a recent paper Long and Seibert³ give the results of their study of 18,744 students, chiefly new entrants, in twenty colleges reporting for the year 1935 to 1936, in whom a strong standard dose of this tuberculin was administered to all those who reacted negatively to an initial small standard dose. They found that from 40 to 60 per cent of students in the eastern and far western colleges showed tuberculous infection, and from 20 to 30 per cent of those in the central states. Since the majority of the students in the various colleges were residents of the district around their colleges the authors believe that their figures reflect the incidence of tuberculous infection among the general population of these regions. High rates were found for New Mexico and southern California, which may be explained by the fact that these regions are popular as resorts for the tuberculous. Because of the denser populations of the east the rates are higher for the students of the colleges in the big cities. In colleges reporting tests on large groups of young men and women of approximately the same average age, positive tuberculin reactions were more common among the men than among the women.

We would like to know, if it can be ascertained, whether tuberculosis is more common among college students than among other classes of the general population. Doubtless much more work will have to be done before we can answer this question, if ever. There is some evidence also for thinking that the strain of a medical course reacts deleteriously on the health of the student. Again we would like to know. Soper and Wilson,⁴ in a study of 3,000 students entering Yale, note that the incidence of tuberculosis was higher in those entering the medical school than in those preparing for professions other than medicine, and their conclusion has been supported by others, notably, Herman, Baetjer and Doull,⁵ and Hetherington

1. *Canad. M. Ass. J.*: Editorials, 1936, **35**: 313; *ibid.*, 1936, **35**: 553; *ibid.*, 1937, **36**: 623.

2. DIEHL, H. S.: *Proc. Amer. Student Health A. Bull.*, 1931, **15**: 128.

3. LONG, E. R. AND SEIBERT, F. B.: The incidence of tuberculous infection in American college students, *J. Am. M. Ass.*, 1937, **108**: 1761.

4. SOPER, W. B. AND WILSON, J. L.: Detection of pulmonary tuberculosis in 3,000 students entering Yale University, *Am. Rev. of Tuberculosis*, 1932, **26**: 548.

5. HERMAN, N. B., BAETJER, F. H. AND DOULL, J. A.: Tuberculous infection in medical students, *Bull. Johns Hopkins Hosp.*, 1932, **51**: 41.

and his associates.⁶ On the basis of observations covering 1930 to 1936 Hetherington and his co-workers found that there is an increase in the percentage of reactors to tuberculin from 85 in students of the first year to 98 or more in those of the graduating class. The third year of the medical course seems to be the most dangerous time for the medical student. There is still much to be done before we can obtain accurate information as to these important matters.

A.G.N.

**The Late Sir Samuel Squire Sprigge, M.A.,
M.D., F.R.C.P., F.R.C.S., F.A.C.S.**

We regret to have to announce the death, on June 17, 1937, of Sir Samuel Squire Sprigge, the Editor of our great contemporary, *The Lancet*.

Samuel Squire Sprigge, the eldest son of a country doctor in Norfolk, was born at Watton on June 22, 1860. He was educated at Uppingham School, Gonville and Caius College, Cambridge, and St. George's Hospital. He became M.R.C.S. in 1886 and took the degrees of M.B. and B.Ch., Cambridge, in 1887 and proceeded M.A. and M.D. in 1904. He was received F.R.C.S.(Eng.) in 1921 and F.R.C.P.(Lond.) in 1927, and elected to Honourary Fellowship in the American College of Surgeons in 1928. He was knighted in 1921 and for his work on the Belgian Doctors' and Pharmacists' Relief Fund was awarded the Medaille du Roi Albert by the King of the Belgians.

Sir Squire Sprigge had close ties with Canada, for in 1895 he married Mab, daughter of the late Sir Charles Moss, Chief Justice of Ontario. Lady Moss is still living in Toronto at the goodly age of ninety-four. Mrs. Sprigge died in 1903 and two years later Dr. Sprigge married her cousin, Ethel, daughter of Major Charles Jones, the gunnery expert. There were two children of the first marriage, a son, Cecil, who is on the editorial staff of *The Manchester Guardian*, and a daughter, married, and at present residing in Toronto, who is a successful authoress, writing under her maiden name of "Elizabeth Sprigge". A daughter of the second marriage, Annabel, is also talented and is living with Lady Sprigge in London. She recently held an exhibition of her drawings and sculpture.

Sprigge, very early, showed literary ability and had no great liking for routine medical practice. Accordingly, after graduation he moved chiefly in London literary circles. He became private secretary to Sir John Russell Reynolds, a leading London physician, and, later, secretary to the Society of Authors, of which

he eventually became chairman. At the Savile Club he associated particularly with Edmund Gosse and William Hunt, the historian, and was on dining terms with the leaders of the "aesthetic" literary movement. He treasured also the friendship of Anthony Hope Hawkins, and Rudyard Kipling, and, a few years later, that of Max Beerbohm, William Rothenstein, and his wife's uncle, Robert Ross.

During this time he wrote for many newspapers and periodicals. One of his early and favourite works was "The Princess Early Pearl", a satire in verse on vegetarianism, published in *The Idler*. He published during this period a number of short stories ("Odd Issues") which brought him much praise. While secretary of the Society of Authors he composed a combative work on copyright entitled "Methods of Publishing", 1890. With Sir Walter Besant he went on a lecturing tour in the United States. At the end of 1892 he was invited to join the editorial staff of *The Lancet* and soon exhibited there his characteristic energy. At the request of the Editors, T. H. Wakley, F.R.C.S. and Thomas Wakley, L.R.C.P., son and grandson of the founder, Sprigge entered upon the task of tracing the history of *The Lancet* from its foundation and the stormy career of its founder. This excellent piece of work came out in serial form in the journal and appeared later in book form as "The Life and Times of Thomas Wakley". It is a mine of information in regard to things medical during the first half of the nineteenth century. In 1905 a series of anonymous articles from his pen were accepted as a thesis for the Cambridge M.D. and was published in book form as "Medicine and the Public".

With the death of Thomas Wakley the third in 1909 Sprigge became editor of *The Lancet* in name, as he had long been in fact, and he served that great journal faithfully and well. In 1928 he revisited Canada and the United States and gave the annual Hunterian Lecture to the American College of Surgeons. He took the opportunity on that occasion to study medical education in North America and published a report of his tour as a special supplement to his journal.

The *British Medical Journal* says of him:—"By nature clear-cut and by habit undemonstrative, Squire Sprigge had no use for sloppiness or gush. But he felt and inspired real affection, and thought much about his friends and helped them with both hands when need arose. Wit and humour do not always go together: 'S.S.S.' had both, and a keen appreciation of them in other people. He was a most stimulating and delightful companion at work or at play; a wise counsellor; a loyal son of his school, his college, and his hospital; and above all things faithful to the great journal which he served for forty-five years."

A.G.N.

6. HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M. AND OPIE, E. L.: Further study of tuberculosis among medical and other university students, *Arch. Int. Med.*, 1935, 55: 709.

Men and Books

THE WHOLE STORY OF CLINICAL RESEARCH IN A NUTSHELL*

BY REGINALD FITZ, M.D.

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Lecturer on the History of Medicine,
Harvard University,*

Boston

It is a peculiar thing that dreams sometimes remain fixed in one's mind for long periods of time. I still remember with uncanny distinctness a dream that I had a few summers ago at Murray Bay. At the time I was playing golf pretty regularly with your late Professor of Medicine, Dr. Campbell P. Howard. It was our custom to battle each day on the golf links and of an evening to play bridge—all on a strictly competitive basis and very seriously. The third hole on the Murray Bay golf course is a short, blind hole. One is supposed to pitch up a hill to the green, to climb the hill slowly, and to find one's ball within easy putting distance of the flag. Surprising things may happen, however, between the time the ball leaves the tee and gets into the cup.

One night, after a particularly happy day of golf and bridge, I went early to bed and presently dreamed that Dr. Howard and I were playing golf. We made unusually brilliant drives to the third hole and walked up the hill to retrieve our balls. When we got to the top of the hill I went to my ball and Dr. Howard went to his. Meticulously we went through the formalities of the putting green without speaking to one another, and having halved the hole in three, started for the fourth tee in perfect silence as though we were on anything but friendly terms.

As we strolled along together, suddenly we were joined by a strange-looking, white-headed old Beaver who, apparently, had been watching our putts with considerable entertainment. He was dressed in a somewhat unorthodox costume. He wore, by way of a shirt, a sort of night-gown arrangement which flapped in the wind, and beneath this a pair of cotton bags over very flashy golf stockings, his feet encased in dirty, white sneakers. I felt certain that I had never seen the man before, and thinking that he must be one of Dr. Howard's Canadian friends, and knowing Dr. Howard's politeness, I waited to be introduced. Nothing happened. We three walked abreast toward the tee until finally the stranger remarked, "Gentlemen, I

perceive that you do not recognize me". As far as I was concerned this was a true statement, so I said nothing. Presently the stranger presented himself. "My name is Æsculapius", he said. "May I join you for a time?"

By now we had reached the fourth tee. Just here there is a fine view of the Saint Lawrence River which to me is one of the loveliest spots in Canada. It happened that there were people ahead of us so that we could not drive, so we sat down on the bench just back of the tee, stretching out our legs. Tobacco seemed indicated.

Æsculapius pulled out a seedy-looking briar, puffed at it meditatively for a few minutes, and then enquired, "How goes the practice of medicine down here nowadays?" Dr. Howard answered, "On the whole, pretty well I think, but occasionally I have my doubts. It seems to me that the laboratories are tending to do away with good clinical observation to a certain extent, and that of late we have changed the breed a little too quickly and perhaps are turning out from the medical schools technicians rather than doctors. Sometimes I fear a mechanized medicine and wonder what will happen in the future".

Æsculapius seemed amused by such a point of view. "My dear chap", said he, "Don't you realize that I've been hearing that kind of talk for the last thousand years? Why, I fixed the future of medicine a long time ago. It is written in the book of the Gods that great doctors shall appear from time to time to offset any thing that mere mortals can do to upset the progress of clinical medicine." This sounded to me like a pretty broad statement, and I dare say that Dr. Howard, too, looked incredulous. For presently Æsculapius went on, "Have you never heard of the Iron Men?" Dr. Howard and I shook our heads. "Well, after all", said Æsculapius, "Perhaps it's no wonder. I've been playing with the Iron Men for only a hundred and fifty years or so, and maybe my experiments with them are not generally appreciated. Perhaps you'd like to hear about them?" To be sure, it was a lovely morning for golf, but on the other hand, never having actually seen Æsculapius before, it seemed foolish when one met him not to listen to what such a well-known character had to say. So Dr. Howard and I settled down, and, with the sun at our backs and the woods and hills of Murray Bay all around us, we heard the following tale.

Æsculapius, it appeared, believed in the experimental method. For several centuries he had listened to complaints about doctors, that they were not improving or were even deteri-

* An address presented at a meeting of the Osler Society of McGill University, on January 30, 1937.

orating, and finally he had decided that some method must be devised to make all doctors forever wish to do better work. He had hit upon the following technique which, in his experience to date, had proved entirely efficacious. He had prepared a silver-coated iron pill which he had so endowed that whoever received it was compelled to take an interest in the medicinal use of iron and, at the same time, to advance signally all medical knowledge. It had entertained Æsculapius ever since he started his experiment to give the pill to men in successive generations with very different backgrounds. "For", said he, "It makes no difference to whom I give it. In all the years to come whoever receives it will always be recognized as a great clinical investigator and, above all, as a great doctor. He will have to make his contributions to medical knowledge by shrewd observation, perseverance and honesty, and always by the clinic rather than through the laboratory. So Iron Men will appear from time to time, whenever I think it necessary, and they will keep alive the spirit of clinical investigation in spite of all that you foolish mortals do to the contrary. With Iron Men at work as they are needed, I believe the future of clinical medicine will always be reasonably safe."

The first Iron Man, it appeared, was a Frenchman. Æsculapius said that in 1774, when he first began his experiment, he had flipped up a coin over a large map of Europe. The coin had come to rest on the town of Nîmes, a small city in southern France on the Rhone. Here, in very simple surroundings, he found a plump, healthy-looking baby and had inserted the iron pill in his fist. When it was proper, the baby was christened Pierre by proud Father and Mother Blaud, and in due time he grew up. Of course, as soon as he could talk, Pierre Blaud made it known that he was to be a doctor, and it seemed almost a matter of course for him to go to the University of Paris for his medical training. After he received his degree he came home and finally settled in the neighbouring village of Beaucaire and began to practise medicine. He was perhaps a little pompous and over-dignified for a man of his build, as he was short and thick-set and rather chubby-looking. His friends used to laugh at him behind his back because he seemed affected. For instance, there was a very insignificant hospital in Beaucaire, and Blaud, as soon as he got on its staff, began to copy the Parisian manner and sign his prescriptions "P. Blaud, Physician to the Hospital in Beaucaire". However, it soon became evident that he was an unusually competent clinician, and before long his opinion was highly respected up and down the Rhone valley. He had another interesting characteristic, too, which made his friends in this very sociable community shrug

their shoulders. Instead of sitting around and enjoying the lighter side of life after a hard day's work he spent his spare moments in reading and studying and making careful note of all the peculiar things in medicine that he noticed. Presently he became very much interested in pale people. He observed many young girls and a few young men, too, who had what was generally called chlorosis, and he noticed that they improved remarkably when they were given large doses of iron. Finally he devised an iron pill, and this he administered with surprising benefit.

The year 1831 was a banner year in Beaucaire. For gossip flew around the town that Doctor Blaud had made a medical discovery, and that he had been invited to read a paper telling of it before all the big wigs in Paris, at a meeting of the Royal Academy of Medicine. There was a large gathering to see him off when he climbed aboard the coach that was to start him on his long journey Paris-ward. He looked dignified, no doubt, in his new suit of clothes,

REVUE MÉDICALE.

CLINIQUE ET MÉMOIRES.

MÉMOIRE

Sur les maladies chlorotiques; et sur un mode de traitement spécifique dans ces affections,

Présenté à l'Académie royale de médecine le 23 août 1831;

Par P. BLAUD, médecin en chef de l'hôpital de Beaucaire, membre correspondant de cette Académie, etc.

Les maladies chlorotiques forment un ordre d'affections qui n'ont point encore fixé l'attention des praticiens. Rapportées soit à des lésions organiques internes, à des engorgemens viscéraux, ou à des irritations chroniques, comme symptômes ou simples effets sans importance, elles n'ont pas encore été étudiées dans leur nature intime et dans leur rôle morbide, si actif pourtant. La chlorose exceptée, maladie qui n'en est qu'une forme particulière, toutes les autres variétés de ces affections ont été confondues avec une foule de lésions diverses, qui en diffèrent néanmoins essentiellement. La chlorose elle-même n'a pas été considérée sous son véritable point de vue; elle n'a été généralement regardée que comme un symptôme, ou plutôt un effet d'une autre affection, l'aménorrhée, tandis que le plus souvent elle en est la cause, ou n'a avec elle que des rapports indirects. Ne la

Mars 1832. Tome I.

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Fig. 1.—Title page of Pierre Blaud's paper describing his pills and their proper use. (Boston Medical Library).

a little self-conscious and grave as he started, and all the village talked for days of how at last a citizen of Beaucaire was going to tell the Paris professors something that would make them sit up and take notice. And so Blaud read his paper on "Chlorosis and its Specific Method of Treatment" before the Royal Academy of Medicine in Paris on August 23, 1831.

It was a good paper, one of the best, in fact, describing very simply almost everything we now know about that disease which, for some reason, we like to call by the complicated name of chronic hypochromic anæmia; and he even described how uterine hæmorrhage may at times be a manifestation of this disorder—a discovery to be re-discovered nearly a century later by another Iron Man. But mainly the paper told of the use of iron in the treatment of hypochromic anæmia—iron in large doses, often repeated, and given according to a systematic schedule.

The unfortunate thing is that the learned men of Paris paid but scant attention to Dr. Blaud. Apparently his paper was one of those which falls flat at a medical meeting; perhaps there was a little perfunctory applause, but certainly no real enthusiasm. Dr. Blaud, no doubt, thought of his friends in Beaucaire, how much they expected of him, and how disappointed they would be to hear of his inadequacy, but nevertheless he was compelled to return home without the plaudits of the Parisian medical profession ringing in his ears.

I think he always felt a little bitterly toward Paris. A medical man has to be thoroughly annoyed and cynical to burst into verse, and this may explain why Dr. Blaud in his latter days wrote a satiric poem which pretty well shows his feelings. Some of it is worth reading. It sounds very modern, and makes one feel that doctors and human nature change very slowly.

HOW TO SUCCEED IN MEDICINE*

If by chance 'tis for money, as well as for fame,
With a deep burning ardour your soul is aflame,
To fulfill this desire, complete, without fail,
My advice you must follow in every detail.

Keep away from the town where you've family ties.
Of all my advice, I regard this the most wise.
No matter how learned you happen to be,
Your friends will prefer some stranger to see.

If you wish to eclipse all the men of your age,
You must copy the manners of some wise old sage.
Be ponderous, walk with a dignified tread,
Though even there may be no thought in your head.

At once get yourself a large sporty car,
For Fashion demands that you look like a Czar.
The success of a doctor can ne'er be complete.
If he travels by railroad, or walks on his feet.

* L'Art Médical was written anonymously by Dr. Blaud and published in 1843. I apologize to Dr. Blaud and to Æsculapius for a very free rendering of these few stanzas. Æsculapius quoted them in French and spoke very quickly.

Take pains, when a patient comes under your care,
That his family knows of his life you despair.
If he dies, you've forewarned them; on you there's no blame.

If he lives, fame and glory attach to your name.

Elect to prescribe only drugs that are rare;
The costlier, too, the better you'll fare.
Always choose things with a strange foreign name,
Instead of home remedies whose effect is the same.

See often rich people who imagine they're ill,
With an obscure disorder that's helped by your pill.
Such patients not only are kind to their nurse,
But often replenish a poor doctor's purse.

Be sure that you advertise in every known way;
Tend meetings, talk loudly, let newspapers say
In flattering terms that your speeches are grand.
The first thing you know you'll be much in demand.

Such is the kind of a life you must lead,
If in this day and age you're in hopes to succeed.
If you do as I've said, and perpend what I mean,
You'll become a Professor or maybe a Dean!

Dr. Blaud published several other papers on a variety of subjects during his lifetime, but certainly it was the paper on the therapeutic use of iron and his description of Blaud's pills, each to contain 25 centigrams of sulphate of iron, that was his contribution to medicine as an Iron Man.

Æsculapius admitted that he was a little hard put to it at first to make the medical world



Fig. 2.—The label from a bottle of Blaud's pills.

recognize the importance of the work. "But", said he, with a twinkle in his eye, "I found a way all right". It seems that Dr. Blaud had a devoted nephew, a youth who thought the doctor was the greatest man in the world. Not having quite the necessary education to become a doctor, he decided to follow in his uncle's footsteps as best he could, and therefore became a pharmacist. When he heard that Dr. Blaud was going to Paris, he had a fine idea. He knew that the doctor had been using an iron pill, and was going to describe how it should be made and administered; he felt sure that it would be successful and in great demand, so it seemed to him that these pills might well be manufactured by the family and

sold in bulk, thus bringing not only fame but also fortune to the Blands of Beaucaire—and so the true, veritable, silver-coated pills of Dr. Bland, made in Beaucaire by his nephew A. Bland, pharmaceutical chemist, came into general use in the middle of the nineteenth century and have been helpful to countless pale people all over the world ever since.

The second man to be given the pill, said *Æsculapius*, was a German, and a doctor's son, for it seemed proper to keep reminding people that there was such a thing as an inheritable tendency to practise medicine successfully. Felix von Niemeyer was born in Magdeburg in 1820. He wished to follow in his father's footsteps, and accordingly received his medical education in the University of Halle, had post-graduate work in Prague and Vienna, and then, at the age of twenty-four, returned to the city of his birth expecting to spend the rest of his days there in the general practice of medicine as had his father before him. But the silver-coated Iron Pill allowed of no such placid living. In the first place, Niemeyer soon discovered that he was possessed of a restless activity which even a rapidly growing practice could not satisfy. In the second place, a great epidemic of cholera visited Magdeburg shortly after he had opened his office there, and inspired him with a desire to study the disease in order to recognize it early and treat it effectively. In the third place, by virtue of soon being placed in charge of the Medical Division of the Magdeburg Town Hospital, he discovered that he had in him something which seemed to impel him to teach.

Shortly after he received the appointment to this post he began to write clinical papers on various subjects and to give lectures and clinics to the doctors in the neighbourhood. Presently older men in other parts of Germany began to hear of him, to shake their heads knowingly, and say to one another over a glass of beer that up in Magdeburg there was a young chap called Niemeyer, son of old Dr. Niemeyer there, who certainly had original ideas on medicine and ability to express them. Some university, they said, ought to snap him up and give him a chance. So it happened that when he was thirty-five years old, he was invited to become Professor of Special Pathology and Therapeutics in the University of Greifswald and Director of the Medical Clinic there. To be sure it was not much of a show according to modern ideas. But in spite of being handicapped by lack of funds and lack of equipment Niemeyer very promptly made himself felt and soon built up a first-rate university clinic in that small centre.

An Iron Man later was to say, "Work is the Master-Word in Medicine". Certainly Niemeyer believed this. Each morning at 4.00

o'clock he began his day's work, spending the early morning in reading and writing. Eight o'clock found him at the clinic, where until noon he held ward-rounds, gave lectures or demonstrations, or visited his assistants in the laboratories. He spent the afternoon in seeing private patients, and he worked at his desk again until far into the night. Day by day he became increasingly popular; all the patients liked him and he had the ability to inspire even the dullest student with a desire to learn—an essential attribute of any great clinical teacher.

In 1858, when he was only thirty-eight years old, was published the first volume of his two-volume textbook, "*Lehrbuch der Speciellen Pathologie und Therapie*", which henceforward was to be republished in many successive editions and was to be translated into almost every language. Nearly all medical students



Fig. 3.—Felix von Niemeyer. "I owe the rapid growth of my practice to Bland's pills". (Boston Medical Library).

the entire world over between 1860 and 1890 were familiar with this book and swore by it with the same fervency that the students of the next generation were to swear by Osler's "*Practice of Medicine*".

In 1860, when Niemeyer was forty years old, he was called to the chair of medicine in Tübingen, and there, in that lovely university town, he spent the rest of his days, always working hard and enthusiastically, training generation after generation of students and assistants, writing, and making his name and the name of the University of Tübingen among the greatest in the world. When the Franco-

Prussian War broke out, he naturally conceived it his duty to drop his work in order to become a medical officer in the Prussian Army; and having served his country with distinction, he returned to Tübingen, to pick up again the threads of university life as though nothing had happened.

"I take off my hat to Niemeyer", remarked Æsculapius. "He did almost everything that a decent doctor could do to help medicine. The world couldn't have a better example of how one of our profession should behave as a private individual in university life and as a public-minded patriot in times of national stress. I made no mistake in giving him the Iron Pill."

The third man to receive the pill was a Canadian, born in 1849, and was a graduate of the McGill Medical School and at one time Professor of Medicine here.

Æsculapius told Dr. Howard and me that he had always liked Canada and McGill; there was something about McGill that to him had the warming flavour of Scotch whiskey—a concoction that he found peculiarly palatable; he liked the conservatism of McGill, too, and the fact that the Medical School was largely contented to follow along the Edinburgh tradition and turn out good clinicians without too rapid introduction of new-fangled contraptions for improving medical education. But he had felt that in some ways McGill was a little too slow in a new country and perhaps needed shaking up from time to time. So it had seemed wise to him, toward the end of the nineteenth century, to prescribe for this medical school a strong tonic to be used regularly, and this he had done by endowing it with the best Iron Man of all, an Iron Man triply gifted; with the Iron Pill to insure clinical investigation; with a gold Eversharp pencil so that he should write happily of what he knew; with the quality of affectionateness in his character so that people the entire world over should love him.

It would be presumptuous for an outsider at a meeting of the Osler Society of McGill University to speak of Sir William Osler, of his background, his education, his accomplishments and his influence. To describe the ingenious manner in which Æsculapius wove him into the pattern of the Iron Men is, however, perhaps permissible. Ever since the days of the earliest incunabula, Æsculapius had watched the growth and development of medical books with keenest interest. The gradual formation of university libraries had pleased him, but he had often chuckled over the recent amazing growth of medical journalism, believing that many of the papers that were published in modern times had better never have been written. When a really good book came along, however, he

thought that, like a good medical family, it might advantageously be perpetuated.

Niemeyer's book seemed to him to have served a very useful purpose. The first edition in German had been published in two volumes between 1858-60, and subsequent editions were printed every two or three years later, to meet the demand for them, until the eleventh edition appeared in 1885, some fifteen years after

William Howard M.D.

Dec 29, 1855 A TEXT-BOOK OF *City Hospital.*

PRACTICAL MEDICINE,

WITH PARTICULAR REFERENCE TO

PHYSIOLOGY AND PATHOLOGICAL ANATOMY.

BY

DR. FELIX VON NIEMEYER,

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TRANSLATED FROM THE EIGHTH GERMAN EDITION, BY SPECIAL PERMISSION OF THE AUTHOR.

BY

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ONE OF THE PHYSICIANS TO TRINITY HOSPITAL, MEMBER OF THE NEW YORK COUNTY MEDICAL SOCIETY, FELLOW OF THE NEW YORK ACADEMY OF MEDICINE, ETC.

AND

CHARLES E. HACKLEY, M.D.,

ONE OF THE PHYSICIANS TO THE NEW YORK HOSPITAL AND TRINITY HOSPITAL, MEMBER OF THE NEW YORK COUNTY MEDICAL SOCIETY, ETC.

REVISED EDITION.

VOLUME II.

NEW YORK:

D. APPLETON AND COMPANY,
1, 3, AND 5 BOND STREET.
1883.



Fig. 4.—Title page of a late Appleton edition of Niemeyer's textbook. (Harvard Medical School Library).

Niemeyer's death. In 1869 an edition, translated into English by Dr. George H. Humphreys and Dr. Charles E. Hackley, of New York, had been published by D. Appleton and Company, and this proved so successful that subsequent editions of it were necessary in 1870, 1871, 1874, 1875, 1878, 1879, 1880, 1881, and 1883. Obviously, any book that was still popular and sought after in a foreign language for many years after the author's death must have had in it a great many unusual qualities. Æsculapius said that he himself had always a great fondness for the book, partly because of what it said in each reprinting concerning the use of iron in the treatment of chlorosis.

"If any medicine ever deserved the name of a specific, iron does, as a remedy in this disease. Opinions vary greatly as to the proper form and dose of iron. For more than twenty years I have used *Blaud's* pills almost exclusively in chlorosis, and have witnessed such brilliant results from them, in a large number of cases, that I have never found any opportunity to experiment with other articles. Instead of the forty-eight huge boli, according to *Blaud's* original prescription, I have ninety-six pills made. Nor am I so timid in increasing the dose according to *Blaud's* formula, but order three pills thrice daily, and sometimes four or five if they are well borne, which they almost always are. Three boxes of *Blaud's* pills nearly always suffice to cure the most persistent chlorosis. At Magdeburg and Greifswald I often had to send my recipe for the pills to a great distance, my good fortune in the treatment of chlorosis—to which, by the bye, I owe the rapid growth of my practice—having given me a great reputation as the possessor of a sovereign remedy against that disease. I do not suppose that *Blaud's* pills excel all other ferruginous preparations in virtue; indeed, I have repeatedly satisfied myself that colleagues who made use of other recipes obtained equal results, provided only that they gave doses of equal size; but I also believe that the efficacy of *Blaud's* pills cannot be surpassed, simply because they can be administered in very large doses without distressing the patient."

About 1885, however, the Appleton Company, at least, began to realize that no longer would there be much use in continuing with the Niemeyer book. Probably the critics said it was becoming out of date, and its sales began to fall off in a disheartening way. Hence, before long this publishing house began to cast around for some new author who might be found to write a new book to succeed Niemeyer's, and which might prove equally useful and popular over a long period of time, and be just as profitable. Æsculapius, of course, was thoroughly cognizant of the situation and immediately thought of the third Iron Man and his gifts. And so, in the fall of 1890, Dr. Granger, Messrs. Appleton's agent, went from New York to Baltimore to see Dr. Osler and finally inveigled him into preparing a textbook. Osler wrote, "We haggled for a few weeks about terms and finally, selling my brains to the devil, I signed the contract". Æsculapius roared with laughter. "Of course it wasn't the Devil that was plaguing Osler", said he, "It was only I!"

The first edition of Osler's, "The Principles and Practice of Medicine" appeared in 1892. It was published by D. Appleton & Co. Its general appearance and typography was strikingly like that of the last American edition of the Niemeyer book. Like the Niemeyer book, it was brilliantly coloured with the personality of its writer, and immediately achieved universal popularity. And as for taking an interest in the medicinal use of iron, in all the years that new editions appeared during Sir William's lifetime, it always was stated:

"The treatment of chlorosis affords one of the most brilliant instances—of which we have but three or four—of the specific action of a remedy. Apart from

the action of quinine in malarial fever, and of mercury and iodide of potassium in syphilis, there is no other remedy the beneficial effects of which we can trace with the accuracy of a scientific experiment. It is a minor matter *how* the iron cures chlorosis. I have for years, in the treatment of chlorosis, used with the greatest success *Blaud's* pills, made and given according to the formula in Niemeyer's* textbook, in which each pill contains two grains of the sulphate of iron. During the first week one pill is given three times a day. In the second week, two pills, in the third week, three pills, three times a day. This dose should be continued for four or five weeks, at least, before reduction. An important feature in the treatment of chlorosis is to persist in the use of the iron for at least three months, and, if necessary, subsequently to resume it in smaller doses, as recurrences are so common."

Æsculapius then continued, "Books are very human and may be very much like people. I like to hear of doctors' sons doing well in medicine and carrying on the work begun by their fathers. I have a great fondness for Osler's "Practice of Medicine", particularly because it appeals to me as being the legitimate offspring of Niemeyer's book. The two make a fine father-and-son team—already with a record of more than seventy-five years of continuous service to the medical profession behind them, and still going strong. I dare say that some day I shall have another Iron Man write a grandson to Niemeyer's book, but with Osler's "Practice of Medicine" still so spry and virile as it is at present, there's no real need for a new child just now".

The fourth man to be entrusted with the pill is a product of New England and a dyed-in-the-wool Bostonian. For many years Æsculapius said that he had regarded the Massachusetts General Hospital as having staged one of the most dramatic scenes in the entire history of medicine when on October 16, 1846, ether was first used there to induce anæsthesia. He had always thought well of the medical families of Boston like the Warrens—John, John Collins, Jonathan Mason, John Collins, and John, spanning from father to son a hundred and fifty years of uninterrupted medical progress in the New World, and he had always had a friendly eye on Harvard since her medical school began. And so in 1885, when a great-grandson of his friend Dr. James Jackson, a pioneer professor there, whose "Letters to a Young Physician" had inspired so many medical students, was born, he determined, at the proper time, to pay a compliment to Harvard and the Massachusetts General Hospital by giving that boy the pill to hold. George Richards Minot grew up and took naturally to medicine like a duck to water. He was an honour student at the Harvard Medical School, and as an intern in the Massachusetts General Hospital displayed notable initiative and interest in blood counting and in studying

* Curiously enough, in the 6th edition of 1905, the name appears as "Niemeyr".

anæmic patients. While he was a member of the staff it at once became apparent to even the most unobservant that Bland's pills had suddenly acquired a most extraordinary popularity in the hospital. When finally in 1926, at

They make things go. When all's said and done, to have people like them around and at work every once in so often is the whole story of clinical research in a nutshell."

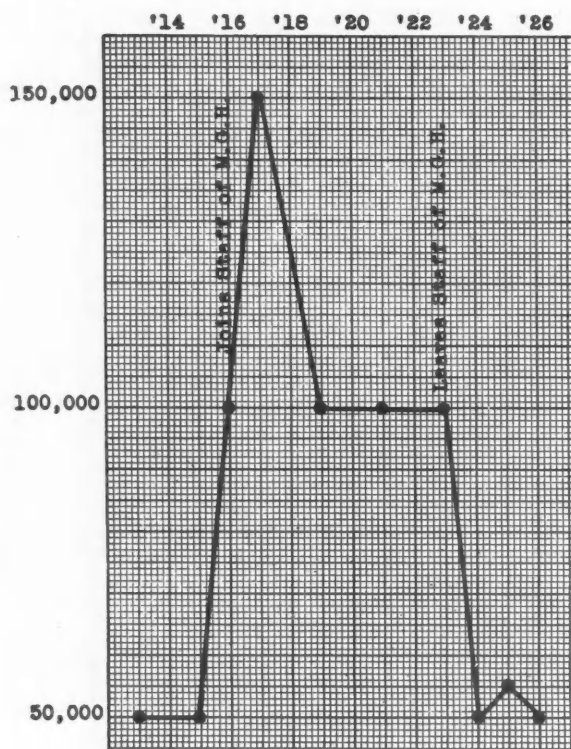


Fig. 5.—The annual consumption of Bland's pills at the Massachusetts General Hospital while Dr. Minot was a member of the staff.

a meeting of the Association of American Physicians, Dr. Minot read his paper "Observations on Patients with Pernicious Anæmia Partaking of Special Diet" and showed that pernicious anæmia to all intents and purposes was henceforward to be a curable disease, Æsculapius said that he felt very proud and happy. This latest accomplishment of the Iron Men seemed to him amply to justify all the time and thought he had put into this experiment. He was determined to keep on with it for a few centuries longer.

"Of course", said Æsculapius, "It's nice that you people down here recently have had sense enough to give me a Nobel Prize for the work of one of my Iron Men. That you have done this shows that you have rather more discernment than I credited you with. Recognition of that sort doesn't count for very much though; in my opinion, what really counts is the way in which the Iron Men behave while they hold the pill. A prize is only of temporary value and like as not is soon forgotten. I've a bunch of prizes hidden away somewhere in a closet up on Olympus and they mean very little to me. The Iron Men, however, will be remembered forever and their influence will always be felt.

Dr. Howard and I played golf together the next morning and he beat me very badly. For when I got to the third hole I began to think of Æsculapius and the Iron Men. I have been thinking a good deal about them ever since, until I have begun to wonder whether what the old gentleman said to Dr. Howard and me that morning in Murray Bay was not something more substantial than a dream. Certainly, all medical students should believe his story. For some student, in some medical school, just about now, almost surely, is the Iron Man of the next generation, the fifth Iron Man, and already he may be marked to receive the pill. Should he be at this meeting, let him realize the responsibility that goes with the gift of being able to do original work in medicine, and how much is expected of him because he has it. Good luck to him. When his turn comes, for the sake of all of us, may he properly carry on the traditions of the Iron Men.

Association Notes

The Annual Meeting

The Sixty-eighth Annual Meeting of the Canadian Medical Association, in conjunction with the Fifty-seventh Annual Meeting of the Ontario Medical Association, was held from June 21st to 25th in the City of Ottawa. As generally happens when the place of meeting is in some central place, the attendance was excellent. The Chateau Laurier, the Headquarters, proved an ideal locale for such a large gathering, its spacious public rooms and corridors lending themselves admirably to the purposes of the two Associations. Taking a leaf out of the book of the Ontario Medical Association, the Canadian Medical Association sponsored a Scientific Exhibit which was of great interest and drew high commendation. The educative value of such exhibits is, some think, even greater than that of the formal papers, and there is no doubt that the innovation has come to stay. It should not be overlooked, however, that to stage these encroachments considerably on the finances of the Association. The Commercial Exhibits were very well set up and were so located that it was easy to explore them. The attendance of members and visitors was highly satisfactory, topping the 2,000 mark.

On June 18th the Executive Committee met in a two days' session and prepared the business for submission to the Executive Council, which

convened on June 21st and 22nd. Much business was advanced, and in due course members will be more precisely informed as to what transpired.

The Association was gratified to learn that His Majesty King George VI had been graciously pleased to extend to it his patronage. A pleasing feature of the meetings was the presence of three fraternal delegates, Sir Harold Beckwith Whitehouse, of Birmingham, Mr. R. Watson Jones, of Liverpool, representing the British Medical Association, and Dr. W. Cutter, of Chicago, representing the American Medical Association. The British and Canadian Medical Associations are affiliated bodies and a strong sentimental bond exists between them. A feeling is existent that we could, with advantage, make this bond still stronger, and steps are being taken looking towards this end. The greetings of the British Medical Association to its Canadian brother were brought by Sir Beckwith Whitehouse, and read in part as follows.

"In particular, the (British) Association is proud to observe that the Canadian Medical Association is taking an active and statesman-like concern in the development of medical policies which relate to public health and to the organization of medical services, and here, as in other respects, the cultivation of close and confidential relations between the two Associations will be mutually helpful." The message was signed by Sir E. Farquhar Buzzard, President of the British Medical Association, and Dr. C. G. Anderson, its medical secretary.

Much of the success of the convention was due to the kindly interest of His Excellency Lord Tweedsmuir, who was present at luncheon on June 23rd and addressed the gathering in his inimitable manner, and, again, was present at the General Public Meeting and the President's Reception which followed. The interest of the Government in the work of the Association was expressed by the Hon. C. G. Power, Minister of Pensions and National Health, who spoke at the Luncheon given by Dr. T. H. Leggett, the President-elect to members of Council on June 21st. His Worship Mayor Stanley Lewis presented the key of the City (in wood) to Dr. Leggett, though, as he humorously remarked, the latter could probably get into any part of the city without a key!

On the evening of June 22nd the Ottawa Medico-Chirurgical Society were hosts to the Council of the Canadian Medical Association. Dr. R. Lorne Gardner, the president, proposed the toast of the Canadian Medical Association, which was responded to by Dr. George S. Young, of Toronto, Chairman of Council. Dr. H. B. Moffatt, of Ottawa, proposed the health of the guests which was responded to by Sir Harold Beckwith Whitehouse, of Birmingham, Prof.

Antoine Lacassagne, of Paris, and Dr. W. Cutter, of Chicago.

The high light of the Convention was the General Public Meeting, held on Wednesday evening, June 23rd. This presented a brilliant scene and many on the platform wore academic and official robes and the ceremonial adopted by the Association for this occasion was carried out. Honorary memberships were conferred on our distinguished visitors, Sir Beckwith Whitehouse, Mr. R. Watson Jones, Prof. Antoine Lacassagne, and Dr. John S. Lundy. The retiring president, Dr. Hermann Robertson, of Victoria, installed the new president, Dr. T. H. Leggett, of Ottawa, and was himself invested with the handsome Past-president's badge.

On Thursday, June 24th, Dr. Robertson gave his valedictory address, which is here given, practically *in extenso*, as it covers admirably the more important efforts of the Association during the past year. The past-president spoke as follows.

After thanking the Ottawa members of the profession for their excellent work in staging the Convention in all its details, Dr. Robertson continued.

"In choosing a subject for a valedictory address one is confronted with the difficulty in deciding what may and what may not be of interest to the general profession, so I trust you will bear with me if, by any chance, old bones of contention are resurrected for critical discussion. Certain matters of vital importance to Canadian Medicine will be brought under review, because, without a strong skeleton as a weight-bearing support, the body of medical activities cannot be expected to advance normally in upholding the dignity and usefulness of the Canadian physicians, in whose hands is placed the responsibility of looking after the health of the citizens of our country.

"The early history of the formation of the Canadian Medical Association contains many interesting details which demonstrate the eagerness of the medical men, then resident in Canada, to establish a National organization having for its various objects the placing of all medical men upon the same plane, and the humane desire to make concentrated efforts to assist in alleviating the plight of the sick man.

"It is appropriate at this juncture to comment on the fact that at a meeting of the licensed medical practitioners of the District of Dalhousie and Bathurst, Canada West, and Sydenham, Canada East, held at Bytown on December 14, 1844, suggestions were made to the editors of the *Montreal Medical Gazette* that support should be given to the general trend of thought contained in a communication printed in that journal and emanating from Dr. Joseph Painchaud, of Quebec. Accordingly, Bytown (the then name of Ottawa) was associated in the early attempts to bring about a federation of the medical practitioners of Canada.

"The birth of the Dominion of Canada, however, in 1867, brought about by the British North America Act, afforded a natural opportunity to attempt the organization of the medical profession. An organization meeting of medical men was held in Quebec City, October 9, 1867, in the Grand Hall of Laval University. Dr. James Sewell, President of the Quebec Medical Society, was Chairman, and his address as recorded had as its main theme the following: 'We are not seeking our own aggrandizement nor our own individual advance; we

desire to promote the welfare of our fellow men and shall rest content to benefit the mass'—a sentiment which permeates the affairs of our present Association.

"The first annual meeting was held in Montreal, September 2, 1868, and the Hon. Dr. Charles Tupper, C.B., was the first President. No scientific papers were read at this convention, as it may well be understood that there was much business to be discussed arising out of the reports of the various committees which had been appointed at the Quebec meeting the previous year. From this time onward, the Association experienced many difficulties in keeping its head above water, and, indeed, the Great War called a halt to many of its activities, which were eventually resumed at a meeting held in Halifax in 1921. From that time the Association has been functioning without a break.

"One of the duties of the President is to visit the Provinces when and where the Provincial Medical Associations are in annual session, to convey to each branch the greetings of Council, and to bring to their notice any matters receiving attention by the parent body, besides enlightening them in regard to doings in the near future. Your President, in visiting Alberta and the Maritime Provinces last August and September, was greatly impressed by the sincerity and eagerness of the medical men to work for the common good, and bring about a solidarity of purpose. The important subject of federation of all Canadian physicians into one composite body was one of the principal subjects under discussion. Everywhere I have met men of the same sort,—earnest and interested, intelligently and actively, in the many problems that confront the medical profession today. Sometimes there have been active differences of opinion as to some policies of the Association, but it would be a poor world in which everybody thought alike, and a poor heaven!

"It is emphasized that there are certain objects of federation, and that these could be summarized as follows. First, there are many medical men living in the country districts who do not enjoy the same privileges as those living in close proximity to cities possessing teaching institutions, where post-graduate study may be pursued under the supervision of trained teachers. In the past, the Canadian Medical Association has sent lecturers to outlying points, where practitioners could enjoy the privilege of witnessing the demonstrations, and listening to the inspiring addresses of some of the leaders of medical thought. As an example one should mention the generous aid of the Sun Life Assurance Company of Canada, which donated \$30,000, annually to the Canadian Medical Association for the above purpose during the years 1926 to 1932. This wonderful gesture of benevolence was, unfortunately, discontinued owing to the force of economic conditions.

"Further, the voice of the profession as a body would carry more weight in all National and Provincial health discussions. As an example of the profession being in a position to speak advisedly, one need only look at British Columbia, where a Health Insurance Act, recently placed upon the Statutes of the Province, was considered by the medical men of British Columbia as an inadequate measure for the relief of certain sections of the laity. The Government of the day has delayed the enforcement of this Act, and it is an assured fact that the strong opposition coming from the Medical Association had a great deal to do with the Government's decision in the matter. It has long been on record that the Canadian Medical Association is in favour of a National Health Insurance Act that would follow the lines laid down in the report of the Economic Committee, which was presented at the Calgary Meeting in 1934. The attitude of the British Columbia medical men, as mentioned above, demonstrates more than ever that the profession in Canada should be bound more firmly together than at present.

"Another great advantage of federation is the fact that the standard of medical education and practice could be more readily attained, inasmuch as every physician could feel that he should be interested in this phase of medical life. The Royal College of Physicians and Surgeons of Canada, which came into being a few years ago, is a direct product of the Canadian Medical Association, and has materially helped to raise the standard of medicine generally, and, it is hoped that the Royal College will take upon its shoulders the responsibility for the designation of specialists in the various branches of medicine, so that graduates in medicine will have placed before them an incentive to train themselves for some particular specialty. This alone cannot fail to result in giving a man a definite position among his brethren.

"The *Canadian Medical Association Journal*, which is the official organ of the Association, contains information of a highly scientific and practical nature. This periodical would carry understanding of medical conditions and the needs of all parts of Canada to our practitioners, and, with federation completed it would be sent to every medical man in Canada.

"The growth and influence of an 'united' profession would materially help to enlist the sympathy of the wealthy, who would be inclined to donate funds for lectures, and scholarships for original work, together with endowments of various kinds. An appeal for financial assistance coming from a federated medical profession of Canada for the prosecution of some philanthropic object, would, it is felt, not fall upon deaf ears.

"Problems which are of particular interest to the profession could be more easily dealt with by a united profession, as there is more direct representation upon the Council of the Canadian Medical Association, each province sending its own elected representatives to the Executive Council.

"If such a scheme as federation could be perfected and carried into effect by all the Provinces the ultimate results would redound to the credit of Canadian Medicine. In such a federation each Province would retain its own autonomy in all provincial matters, and in no particular would the Canadian Medical Association attempt to interfere with the provincial activities. This joint meeting in the Capital City of the Canadian Medical Association and the Ontario Medical Association speaks volumes for the feasibility of this scheme, and, indeed, stresses the importance of the profession being nationally conscious in approaching the great problems facing organized medicine today.

"The scourge of cancer is ever at our doors. The Trustees of the King George V. Silver Jubilee Fund are a national body, entrusted with the work of fighting this disease, and upon the Canadian Medical Association has devolved the duty of prosecuting a campaign against cancer.

"The *modus operandi* has to be worked out in detail, and it cannot be too strongly urged how important it is that medical men should be working under one banner—a federated profession. In the near future a concrete plan of attack will be launched.

"For many years Health Insurance in Canada has been discussed by ruling bodies and individuals. All sorts of plans have been devised whereby the general public could receive the necessary medical care, irrespective of their worldly possessions. It may be taken for granted that medical attention has never been refused to the poor, yet it may be safely stated that the medical man has been carrying on an altruistic work which, probably, should be shouldered by municipal, provincial or federal bodies. In 1935, at the combined meeting of the Canadian Medical Association and Ontario Medical Association a resolution was passed by your Executive that the Federal Government should be approached with

a request for the appointment of a Royal Commission whose duty would be to examine the whole question of medical service to the people of Canada. Following this, at a meeting of the National Public Health Association, a resolution to the same effect was forwarded to the Government then in power, but so far no action has been taken, and I believe that this whole question can only be approached from a national standpoint. From the medical man's point of view (and this need not be construed as selfishness) a certain amount of compensation from responsible authorities should be granted him as payment for professional attention to the poor and indigent. A National Health Act would assure those unfortunates of adequate medical attention, and at the same time relieve the situation of any question of monetary sacrifice, which, under ordinary circumstances, should not be demanded of the medical profession. The persons eligible to benefit from such a scheme would obtain a better medical service when the question of charity does not enter into the engagement. To repeat, the Canadian Medical Association is in favour of a National Medical Health organization, and will lend its full force and influence to a nationally applied scheme, endorsed by a federated Medical Association.

"The Canadian Medical Association has made an exhaustive study of Health Insurance, as noted in the report of the Economic Committee of 1934. In this excellent pamphlet will be found facts and recommendations in the event of a National Health scheme being inaugurated. As an evidence that the Canadian Medical Association is ready and willing to lend its support and advice regarding this question, the General Secretary, Dr. T. C. Routley, was sent abroad this Spring to study 'health insurance' as applied in other countries, such as, England, Germany, Denmark and France. His report has been submitted to your Council at this annual meeting, and I feel I should not anticipate the information which will become public in the next few days. If the Federal Government should at any time undertake the matter of a National Health Insurance, the Canadian Medical Association is in a position now to give the benefit of their advice, in fact, today, our Association, in anticipating such a national movement, has shown a progressive and philanthropic spirit.

"Of the various functions performed by the Canadian Medical Association one of the most important is that of the Department of Hospital Service. This department, which is now in its tenth year, has proved of tremendous assistance in a consultative capacity to the hospital field throughout Canada. It is maintained by an annual grant from the Sun Life Assurance Company of Canada, and its director, Dr. Harvey Agnew, has been kept busy studying hospital and staff problems, making surveys, helping 'sick' hospitals, ironing out staff difficulties and improving medical intern education. This department has been of particular assistance in co-ordinating and interpreting to each other the interests and viewpoints of the medical and hospital fields.

"At the expiration of my term of office as your President, I would wish to express my appreciation of the great honour which has been conferred upon me, and the kindness and tolerance of all officials who have lent their unswerving support to lighten my load. To our new President, Dr. T. H. Leggett, I offer sincere congratulations, and trust that his tenure of office may be as profitable and as happy as mine in helping the cause of our beloved profession."

Halifax has been chosen as the place of meeting for 1938, and Dr. Kenneth A. MacKenzie, Professor of Medicine in Dalhousie University, Halifax, will be the next president.

Hospital Service Department Notes

Routine Instrument Counts

In the preparation of the defence in a medico-legal case in which it was alleged that a surgical instrument had been left in the body, this Department had occasion to check up on the practice in various hospitals with respect to instrument counts. Enquiry was made of a number of leading hospitals in Canada as to whether or not it was routine on their surgical services to have instrument counts as well as sponge counts. A summary of the replies received would indicate that it is not the general practice of the surgical departments in general hospitals to have a routine instrument count. In some of the replies received it was pointed out that it is extremely difficult to make instrument counts routinely, because of the fact that in many hospitals instruments are borrowed from the sterile table for an operation in another room, additional instruments may be called for hurriedly in the course of an operation, and that to be really effective a count would have to be made before the peritoneum be closed, at which time many of the instruments, particularly needles, would still be in use. One teaching hospital does routinely check up on the instruments issued after the morning schedule is completed and before any laundry or other articles are taken from the operating room. Another hospital, although not making a full instrument count, does make a needle count. One large teaching hospital does report an instrument count as well as a sponge count in all operations, and another smaller hospital reports that the instruments are checked before and after each operation.

As the question was asked of representative hospitals in various centres only and was not addressed to all hospitals, there may be others than the two mentioned who do hold instrument counts before and after each operation, but from the replies received such would appear to be distinctly in the minority. Naturally, in all properly conducted hospitals, sponge counts are a routine procedure.

A "Flying Squad" to Combat Maternal Mortality

Still another weapon has been developed in the struggle being waged to reduce maternal mortality. The Birmingham (Eng.) Maternity Hospital has evolved a plan whereby the resources and facilities of the well-equipped obstetrical hospital may be brought to the bedside of the patient suffering from hæmorrhage, shock or other obstetrical emergency at home.

All communications intended for the Department of Hospital Service of the Canadian Medical Association should be addressed to Dr. Harvey Agnew, 184 College Street, Toronto.

This idea of bringing the hospital to the patient avoids the danger and delay associated with the removal of the patient to the hospital.

The "Flying Squad" consists of a mobile emergency outfit, completely equipped with every possible necessity for dealing with obstetrical emergencies, accompanied by a staff nurse who is a trained midwife of the hospital. The hospital has the cooperation of the Birmingham Health Committee and of the St. John Ambulance Brigade, which provides the ambulance for these emergency calls. The consultants of the hospital function in an advisory and consultative capacity. The hospital arranges that some qualified member of the nursing staff will be available at all times to accompany the equipment to the home. Already the experiment has proved of such life-saving value that the trouble and cost have been fully vindicated.

What Duties Should Be Given the Woman Intern?

Whether the intern be man or woman the service expected from this member of the hospital's personnel should not vary. Herein lies the success or failure of the whole system. Many hospitals today are accepting women as interns that ten years ago would not have thought of doing so. There is no good reason why a woman intern should not perform every type of work assigned to a man. Ambulance service, the dressing and catheterization of male patients, and the treatment of all patients who seek relief in the hospital fall within the scope of her work. When a woman applies for and receives an appointment as a hospital intern, and conducts herself as though she expected to be favoured, courted and entertained, she jeopardizes future opportunities for all her professional sisters. Prudery has no place in the life of the hospital. A woman, who, through claims of modesty or physical inability, expects to avoid the performance of any medical duty does not merit either her place as an intern or the high respect which her profession should command. The intern who is a coquette is capable of seriously damaging the morale of a professional staff by her frivolity and selfishness. It is this type who prevent a more widespread adoption of women as interns.—*The Modern Hospital*.

A fool is pleased by flattery (which is deceitful) like the inflated heel of a corpse that has the appearance of fatness. Take heed not to listen to the voice of a flatterer, who expects cheaply to derive profit from thee; if one day thou failest to satisfy his wishes he enumerates two hundred faults of thine.—*Maxim XXX* of the Sheik Sa'di of Shiraz.

Post-Graduate Courses

Post-graduate Course at St. Michael's Hospital,
Toronto, September 13 to 18, 1937

MONDAY

9.30 a.m.—

The management of lung abscesses.—J. H. Elliott and E. A. Broughton.

Anæmias.—H. G. Hall.

Luncheon.

2.00 p.m.—

Certain aspects of anæsthesia.—J. F. L. Killoran, C. G. Bryan, K. M. Heard, and L. A. Stubensey.

TUESDAY

9.30 a.m.—

The management of lobar pneumonia.—J. H. Elliott and E. A. Broughton.

Dermatology.—F. A. Ireland.

Luncheon.

2.00 p.m.—

Ear, nose and throat diseases.

WEDNESDAY

9.30 a.m.—

Review of cases of heart disease.

1. History and physical findings.—A. R. Hagerman.

2. Course progress and treatment.—Dr. McPhedran.

3. Insurance aspects.—T. G. Heaton.

Luncheon.

2.00 p.m.—

Eye diseases.

THURSDAY

9.30 a.m.—

Diabetes mellitus.—D. A. Prendergast.

The significance of diarrhoea.—J. Daly.

The management of duodenal ulcer.—H. Hetherington.

Luncheon.

2.00 p.m.—

Medical cases.

FRIDAY

9.30 a.m.—

Examination of the nervous system.—W. B. Edmonds.

Intra-cranial hæmorrhages.—E. F. Brooks.

The unconscious patient.—J. D. Loudon.

Luncheon.

2.00 p.m.—

Medical cases.

SATURDAY

9.00 a.m.—

The pituitary gland.—N. B. Taylor.

The modern aspects of endocrine medication.—H. G. Hall and D. A. Prendergast.

Luncheon.

Any communications or enquiries should be sent to The Secretary, Department of Medicine, St. Michael's Hospital.

University of Toronto, Faculty of Medicine**POST-GRADUATE COURSE ON PHYSICAL AND
MANIPULATIVE THERAPY**

The University of Toronto, Faculty of Medicine, offers to graduates in medicine a course of one week, commencing Monday, September 20, 1937.

The course will consist of: (a) the presentation of cases showing the clinical conditions requiring these forms of treatment; (b) demonstrations of the methods used; (c) discussions of the indications for each of the methods.

This course will be limited to 20 and will only be given if at least 10 practitioners signify their intention of attending. Applications will be received up to August 15th. Write to the Secretary, Faculty of Medicine, University of Toronto. The fee for the course is \$25.00.

**POST-GRADUATE COURSE ON CARDIOVASCULAR
DISEASE**

The University of Toronto, Faculty of Medicine, offers to graduates in medicine a course of one week, commencing Monday, September 20, 1937.

The course will consist of theatre and bedside clinics and practical work in the wards of the Toronto General Hospital, will be limited to 20, and will only be given if at least 10 practitioners signify their intention of attending. Applications will be received up to August 15th. Write to the Secretary, Faculty of Medicine, University of Toronto. The fee for the course, \$25.00.

POST-GRADUATE COURSE ON FRACTURES

The University of Toronto, Faculty of Medicine, offers to graduates a course of one week, commencing Monday, September 27, 1937, on Fractures.

This course will consist of lectures, demonstrations, clinics, operations and practical instruction on the cadaver. It will be conducted at the Toronto General Hospital, St. Michael's Hospital, the Hospital for Sick Children and the Banting Institute.

The course will commence at 11 a.m., Monday, September 27th at the Toronto General Hospital, and will continue, morning and afternoon, till Saturday noon, October 2nd.

The instructors will be as follows:

TORONTO GENERAL HOSPITAL: Drs. W. E. Gallie, R. I. Harris, K. G. McKenzie, J. A. MacFarlane, D. G. Murray, F. I. Lewis, S. D. Gordon, R. H. Thomas.

ST. MICHAEL'S HOSPITAL: Drs. G. E. Wilson, T. A. Robinson, W. G. Carscadden, D. W. Pratt, J. T. Danis, H. G. Armstrong.

HOSPITAL FOR SICK CHILDREN: Drs. D. E. Robertson, A. B. LeMesurier, J. L. McDonald, W. S. Keith.

The course will be made as practical as possible and an attempt will be made to have the students take part in all demonstrations. The course will be limited to twenty-five.

Applications for admission to the course should be made before September 4th to the Secretary, Faculty of Medicine, University of Toronto, at whose office registration will take place. A fee of \$25.00 will be charged.

**University of Western Ontario, Third Annual
Refresher Course, September 13 to 17, 1937****Surgery****MONDAY**

9.00 a.m.—

Colles' Fracture.—C. C. Ross.

Management of certain conditions of the hip.—R. A. Johnston.

Treatment of the hyperthyroid patient.—A. J. Grace.

V. A. Callaghan.

Cancer of the mouth and lips.—G. McNeill.

Medicine**TUESDAY**

9.00 a.m.—

Some phases of acute chest problems.—G. C. Hale.

The treatment of certain heart conditions.—E. A. Bartram.

Newer methods of diagnosis and treatment of infectious diseases.—F. W. Hughes.

Newer methods of treating diabetes and pernicious anæmia (protamine zinc insulin, liver extract).—E. M. Watson.

Obstetrics and Gynæcology**WEDNESDAY**

9.00 a.m.—

Maternal and fetal birth injuries.—F. R. Clegg.
The management of the common complications of labour.—W. P. Tew.

Clinical Pathological Conference

11.00 a.m.—

Presentation of some interesting pathological specimens.—J. H. Fisher.

Pædiatrics**THURSDAY**

9.00 a.m.—

Common skin diseases of children.—H. J. Loughlin.

Some recent advances in pædiatrics.—K. L. McAlpine.

The less common gastro-intestinal disturbances—pyloric stenosis, pylorospasm, chronic intestinal indigestion.—W. G. Sumner.

Obstetrics and Gynæcology

11.00 a.m.—

Modern pre-natal care.—A. E. Mowry.

Management of post-partum complications.—E. I. Loughlin.

Medicine**FRIDAY**

9.00 a.m.—

The patient with bleeding from the gastrointestinal tract.—J. A. Macgregor.

Recent advances in therapeutics.—F. J. H. Campbell.

Surgery

10.30 a.m.—

Management of renal calculi.—E. D. Busby.

Management of common conditions of the rectum.—H. M. Simpson.

Diagnosis of the painful swollen knee.—G. A. Ramsay.

All sessions will be held in the Lecture Room of the Nurses' Home of Victoria Hospital.

A nominal fee of \$2.00 is charged for registration.

Any registered medical practitioner in good standing is eligible for registration.

All applicants wishing to attend all or part of the course are asked to send in their applications to the Dean's Office before September 10, 1937.

University Notes**University of Manitoba**

Daniel Nicholson, M.D., C.M. (Man.), M.R.C.P. (Lond.), Assistant Professor of Pathology, has been appointed Professor of Pathology in the University of Manitoba to succeed Prof. Wm. Boyd, who has become Professor of Pathology in Toronto University. Dr. Nicholson is the author of "Laboratory Medicine".

At a meeting of the Medical Faculty Council of the University of Manitoba on June 8th, a report of the recent examinations was presented by Dean A. T. Mathers. Of a class of 63 in the first year 8 failed and 4 had honours. In a class of 42 in the second year 2 failed and 3 had honours. In the third year of 58 students 2 failed and 11 had honours. Of 49 students in the fourth year there were no failures and 6 had honours and in the fifth year with a class of 45 there were no failures and 6 received honours.

Professor I. McLaren Thompson and Doctors P. H. T. Thorlakson and C. R. Rice were elected members of the Medical Faculty Council

Executive. Doctors H. D. Kitchen and W. W. Musgrove were elected members from the Faculty Council to the Council of Physicians and Surgeons of Manitoba.

The Dean presented a report on each member of the recent graduating class showing standing in each year and its relationship to the general average of the class.

ROSS MITCHELL

Abstracts from Current Literature**Surgery**

The Treatment of Old Traumatic Bony Lesions of the Face. McIndoe, A. H., *Surg., Gyn. & Obst.*, 1937, 64: 376.

The need for late reparative treatment of these injuries arises chiefly from the cosmetic impairment, and to a lesser extent from loss of function. In the majority of cases these injuries could be treated early with much more efficiency.

The three general principles followed in treatment are replacement, substitution by bone or cartilage, and camouflage by fat or muscle grafts. It is usual to allow six months after arrest of infection before attempting reparative measures, and between the stages of each operation. The author is in favour of bone grafts from the crest of the ilium, although a piece of cartilage or bone from the 7th rib is easier to cut and mould. A circular defect is readily fitted by a piece of the inner compact layer of bone from the iliac fossa, "stepped" into place with wire or chromic catgut suture. The insertion of fat or muscle graft to overcorrect 30 to 40 degrees is generally left for 6 months after replacement or substitution measures. These grafts are inserted through a small incision. The course adopted depends largely upon the general condition of the patient, age, sex, status in life, and the extent of the injury as revealed by supero-mental, 30 degree occipito-mental and small dental x-rays.

In the case of frontal bone injuries involving the outer wall of the frontal sinus replacement is not so safe as substitution. Loss of the supra-orbital ridge is better treated by substitution of iliac crest, with fat graft for final filling. Depressed frontal bone calls for iliac fossa substitution.

With the lateral and depressed fractures of the nasal bones replacement is usually possible during the first 3 weeks. When lateral displacement only is present, refracture, comminution, and resetting of the nasal septum is necessary. Sometimes substitution of iliac crest is more readily performed and more satisfactory than reposition of the septum. With depressed nasal

fractures it is usually necessary to infracture the frontal processes of the maxillæ at their bases in order to correct the marked splaying.

With deformities of the malar-zygomatic compound thorough clinical examination and occipito-mental x-rays are essential for exact delineation. The temporal approach and leverage with a slender osteotome, so useful in simple cases, must be combined with the buccal approach through the canine fossa and the infra-orbital approach, in the cases of tangential applied force. Wiring gives good fixation, but a mass of Stent's compound in the antrum for 10 to 21 days is sometimes necessary for good retention. Adequate drainage into the mouth must be present with the latter retentive measure.

Fractures of the maxillæ may be alveolar or/and much more complex. The alveolæ may be replaced by local pressure or continuous forward traction of the weight and pulley extension type, after refracture. The more severe types, such as the nasal ethmoid maxillary fracture or "dish-face" deformity, and the malar-maxillary fracture, are usually not subjected to other than substitution or soft-tissue graft. In the former the nasal septum and the upper lip require bony support; in the latter, the eye needs to be raised to overcome diplopia.

FRANK DORRANCE

Obstetrics and Gynecology

The Habitual Abortion and Stillbirth Syndrome and Late Pregnancy Toxæmia, Vitamin E and the Prolan-Progesterone Mechanism. Young, J., *Brit. M. J.*, 1937, 1: 953.

The evidence which has become available within recent years is consistent with the view that an important cause of the habitual abortion-stillbirth syndrome, which has baffled the clinician in the past, is a disturbance in the metabolism of pregnancy in which a deficiency of vitamin E is involved. The evidence further raises the question as to the part which vitamin E plays in the prolan-progesterone mechanism of pregnancy.

The clinical applications of the results of recent research are simple and impressive. In this communication some evidence is adduced for the view that the above considerations may likewise supply us with the missing X factor which has been previously postulated to explain the non-toxæmic recurrence of abortion, stillbirth, and accidental hæmorrhage in women who are subject to eclampsia and pre-eclampsia. This evidence is consistent with the view that major degrees of deficiency tend to interruption of pregnancy in the early months without toxæmic manifestations, whereas if the deficiency is less marked the pregnancy is capable of progressing to the later months with a consequent risk of toxæmia. The evidence reviewed in this com-

munication raises the question as to the part played by diet in racial fertility, and, more especially as to how far changes in the consumption of essential dietetic elements may have contributed to the declining birth rate.

ROSS MITCHELL

Contraction Ring Dystocia. Analysis of 36 Cases with Observations on the Use of Adrenalin in 20 Cases. McKenzie, C. H., *Am. J. Obst. & Gyn.*, 1937, 33: 835.

Contraction ring should be differentiated from retraction ring developing in labour because the treatment of each depends on a correct diagnosis. No common factor has been noted in all cases developing contraction rings, i.e., the etiology is still obscure. Adrenalin, assisted by morphine sulphate and deep surgical ether, will relax a contraction ring.

ROSS MITCHELL

Trichomonas Vaginalis Vaginitis. Buxton, R. L. and Shelanski, H. A., *Am. J. Obst. & Gyn.*, 1937, 33: 842.

The incidence of *Trichomonas vaginalis* infestation among patients of the gynecological and pre-natal clinics of the Philadelphia General Hospital was found to be 31.6 per cent. In white patients the incidence was 27.5 per cent and in coloured patients 48.1 per cent. *Trichomonas vaginalis* vaginitis is a clinical entity, and bilateral lower quadrant pain is an occasional symptom. The mode of transmission and the reason for recurrence of the infestation are not known. The use of 1 per cent picrate-kaolin powder, in combination with silver picrate suppositories, is an efficient and simple method of treatment for this form of vaginitis.

ROSS MITCHELL

Pædiatrics

Abscess of the Liver in a Child Nine Months of Age. Wolfson, W. L. and Rothenberg, R. E., *Am. J. Dis. Children*, 1937, 53: 1540.

Pyæmic abscess of the liver occasionally occurs as a complication of intraperitoneal suppuration or, in rarer cases, as a result of focal infection elsewhere in the body. The condition is particularly rare in infants and young children. The authors give references to the scanty literature on the subject.

The case they report was in a boy, nine months old, who was admitted to hospital with a history of fever, marked irritability, refusal to take food, and vomiting of three days' duration. The day after admission an indefinite mass was palpated in the right lower quadrant of the abdomen. On the ninth day of the illness the mass was well developed and readily palpable. At operation an intraperitoneal abscess containing thick foul-smelling pus was evacuated and

drainage effected. Culture gave *B. coli* and *Staph. albus*. The temperature subsided to normal on the fifth day after operation. On the seventh day it was noticed that the umbilicus had become reddened, swollen and tender. Two days later an incision was made into the umbilicus and 10 c.c. of foul-smelling pus were obtained. The child was well for twelve days, when his temperature again rose. The blood count gave 28,000 white cells, of which 74 per cent were polymorphonuclear. Under general anaesthesia a definite fullness in the upper right quadrant of the abdomen was made out, suggesting a mass. Laparotomy was performed, and an abscess was located deep in the substance of the liver. Aspiration revealed pus. As there were no adhesions in the neighbourhood incision of the abscess was left to a later date, though this eventually proved to be unnecessary. Fifteen days after this operation the child was discharged with a healing wound. On two occasions, after the child had left the hospital abscesses developed in the site of the right rectus incision. The liver abscess was in the authors' opinion secondary either to an appendiceal abscess or to suppurative omphalitis. The satisfactory result indicated that it is possible, in young infants at least, to empty a hepatic abscess by aspiration and leave, with safety, the balance of the contained pus to be absorbed or discharged through the puncture sinus along the drains to the surface.

JOHN NICHOLLS

Functional Nervous Diseases in Children.

Hymanson, A., *Arch. Pædiat.*, 1937, 54: 317.

The pathological basis of nervous disorders is still unknown. Clinically speaking, they may be exhibited from early life. Among 280 cases studied by Benjamin one-third showed signs of nervous upset from birth, and 90 per cent developed their symptoms within the first four years of life. In this group the nervous disturbance was quite uncommon after the twelfth year. The causes are both hereditary and acquired. Pende recognizes 22 diatheses which point to a tendency towards functional nervous disease. These, however, can be grouped under six main headings: (1) arthritic; (2) neuro-endocrinopathic; (3) psychopathic; (4) heredosyphilitic; (5) heredituberculous; and (6) heredoneoplastic. Pende remarks, "The two most common diatheses in civilized man are the neuropathic and the psychopathic, which no one perhaps can entirely escape". Hymanson says, "As the child is the epitome of the physical nature of his parents, it is no wonder that 5 per cent of our school children are definitely neurotic". Neurosis in children is much milder than neurosis in adults; many children suffer from some nervous taint at one time or another from which they recover completely. Nervous

inheritance is not an incurable condition. With judicious treatment, and in certain cases with the help of a trained psychologist, the neurosis may be modified and even cured.

JOHN NICHOLLS

Pathology and Experimental Medicine

Differentiation Between Peripheral Arterial and Arteriolar Spasticity in the Selection of Cases for Sympathetic Ganglionectomy.

Perlow, S., *Surg., Gyn. & Obst.*, 1937, 64: 1015.

These experiments were done at the peripheral circulatory clinic, Department of Surgery, Northwestern University Medical School and Michael Reese Hospital.

All measurements were made with the mercury skin thermometer. Arterial spasticity was measured after nerve anaesthetization. Arteriolar spasticity was measured after local injection of histamine. Total spasticity was considered to be measured by the temperature rise following local histamine injection given 30 minutes after nerve block. Normal individuals were tested for arterial, arteriolar and total spasticity by the above methods. In all of them there was a rise, following the injection of histamine, suggestive of the presence of arteriolar spasm not influenced to the full extent by nerve block. In the dorsum of the fifth finger he used sufficient histamine solution (1:2,000 in 0.5 per cent procaine) to produce an intradermal wheal 2 mm. in diameter. In two cases of arteriosclerosis very little rise was obtained proving the organic basis. There was a greater rise in 2 cases of thromboangitis obliterans; a proportionately greater rise with 2 cases of Raynaud's disease, while with one case of acrocyanosis the rise was greatest of all.

The author suggests there is an arterial spasm under the control of the sympathetic nervous system, and an arteriolar and capillary spasm under local control of either a nervous or chemical nature, which is not completely dependent, if at all, upon the autonomic nervous system.

FRANK DORRANCE

Tuberculosis in Wild Voles. Wells, A. Q., *The Lancet*, 1937, 21: 1221.

The belief that tuberculosis in warm-blooded animals living wholly in the wild state is unknown is questioned by the author who reports a widespread occurrence of tuberculosis in voles (water-rats), *Microtus agrestis*. It is known that there is a periodical sudden decrease of the population of these animals in England, and investigations now suggest that epidemic tuberculosis causes this decrease. The Bureau of Animal Population in the University of Oxford

has established a system of live trapping and transport of the voles to the laboratory where they are kept in isolated cages. Autopsies on voles which have died both in the field and in the laboratory show caseous areas in the glandular regions, lungs, and subcutaneous tissues, from which organisms having the morphology of *Mycobacterium tuberculosis* have been grown. Similar lesions have been produced in other voles, guinea pigs and rabbits following injection of this caseous material. The existence of tuberculosis in wild animals may shed new light on the spread of the disease to man and domestic animals, and the laboratory may with profit avail itself of an animal which naturally contracts the disease.

DAVID RODGER

The Action of Adrenaline on Serum Potassium and on the Perfused Liver. The Action of Potassium Chloride on the Blood Sugar. D'Silva, J. L., *J. Physiol.*, 1936, 86: 219, 87, 181. Also Asthma Research Council Report, 1936.

Further studies are reported on the mechanism of the action of adrenaline in the body. The liberation of potassium observed in the intact animal has also been demonstrated in the isolated perfused liver. This is confirmatory evidence that the liver is the source from which potassium is mobilized in the body. Still more interesting is the fact that there is a quantitative relationship between the amount of adrenaline injected and the amount of potassium liberated. Actually, 0.2 mg. of adrenaline mobilizes 24 to 27 mg. of potassium. This will provide a useful means of studying the rate of destruction of adrenaline in the livers of normal and sensitized animals. If this proved the same in both types of animal the focus of investigation would necessarily shift to the method of liberation by the adrenals or to a study of the synthesis of the drug in the body. It has also been found that an injection of potassium chloride lowers the blood sugar, and since adrenaline is destroyed more readily in the intact body than in the perfused liver some factor which aids the metabolic recovery in the intact animal must intervene, and it is not impossible that this is insulin.

ARNOLD BRANCH

Therapeutics

Two Hundred Cases of Eclampsia Treated with Magnesium Sulphate. Stroganoff, W. and Davidovitch, O., *J. Obst. & Gyn. of the Brit. Emp.*, 1937, 44: 289.

A complete study of the administration and use of magnesium sulphate in the treatment of eclampsia is made. Pharmacologists believe that the narcotic and toxic doses closely approximate, being equal to from 1.5 g. and 1.75 g. to 1 kilogram of body weight, yet lower doses are

said to have been fatal. A 5 per cent solution of calcium chloride is an excellent antidote, and should be available when $MgSO_4$ is being used. The routine treatment as outlined was after admission to hospital or after the first fit an injection of 0.015 to 0.02 g. of morphine muriatic and examination under very light chloroform. In 30 minutes about 6.0 g. of $MgSO_4$ was given subcutaneously. About 1½ hours later morphine was again injected, and 3½ hours later 6.0 g. were given again if another fit occurred, and only 4.0 g. if no fit occurred. If no delivery followed the next dose of $MgSO_4$ followed in about 6 hours and was then repeated 8 hours later. No more than 240 g. in 24 hours were used, even if fits followed. Venesection and rupture of membranes and keep patient on right side were advised. In 67.7 per cent of cases the fits were interrupted following the first dose of $MgSO_4$ and continued in 32.3 per cent. A physician always administers the dose. Other drugs such as ledonal, veronal, luminal, and pernocton are being investigated. P. J. KEARNS

On Certain Pharmacologic Actions of the Newer Barbituric Acid Compounds. Gruber, C. M., *Am. J. Obst. & Gyn.*, 1937, 33: 729.

In addition to hypnosis and anaesthesia all these drugs depress the respiratory centre and death may result. Since the respiratory centre is affected before the cardiovascular system, there is a possibility of using artificial respiration to prevent a catastrophe. The second source of danger is the effect on the cardiovascular system. All of these drugs depress the heart muscle. The thio-derivatives appear to be more dangerous than the ordinary barbiturates. The third source of danger is that the rapid injection of any of the barbiturates causes a sudden fall in blood pressure. The changes in the vascular bed is also reflected in the lungs. Acute oedema of the lungs may result, and upon recovery of the animal bronchopneumonia may occur. In human beings as little as 3 grains of nembutal may produce this effect.

In selected cases and if given properly the barbiturates may be fairly safe. In the hands of many, if they are used as anaesthetics in unselected cases, they will be found dangerous both to the mother and to the unborn fetus. They should be given either by a competent anaesthetist or used only as hypnotics. ROSS MITCHELL

Interruption of the Asthmatic Crisis by Tribromethanol (Avertin). Fuchs, A. M., *J. Allergy*, 1937, 8: 340.

In cases of prolonged and severe asthma in which epinephrine fails to relieve a variety of measures may be tried, such as evacuation of pus from infected sinuses, change of environment (hospitalization), 10 per cent glucose intravenously, intravenous sodium iodide, and

the oxygen tent. Morphia may hasten the fatal outcome. In these severe cases the writer has successfully relieved the patient when other methods had failed, by the following means.

Tribromethanol in amylene hydrate (Avertin fluid) was slowly injected rectally, using a syringe on a male catheter. The dose was 50 to 70 mg. per kilo. of body weight (60 mg. was usually effective). Muscular relaxation came as a rule in 10 minutes, but occasionally the effect was delayed for an hour. The patients slept for from one to six hours. On waking they were usually relieved of asthma, remaining so for several days or weeks, and they had recovered their ability to respond to injections of epinephrine.

T. G. HEATON

Radiology and Physiotherapy

Cancer of the Thyroid in Children. Hare, H. F., *Radiology*, 1937, 28: 131.

Six cases of cancer of the thyroid in children under 14 are reported. Primarily, the treatment of all thyroid tumours is surgical—in early cases, for diagnosis and cure; in advanced cases for diagnosis, with tracheotomy when necessary. X-ray treatment of these tumours in children is comparatively recent. All these tumours are radiosensitive, so x-ray is indicated in all cases. The proper lethal dose is to be determined, this dose is close to 3,000 r units. After surgical removal of the tumour as large a dose of x-ray as possible is given over a period of 30 to 45 days, giving a daily dose of 100 r to each unit. Patients are instructed to eat a high carbohydrate diet during treatment, to prevent roentgen sickness. The use of a warm aspirin gargle before meals when the throat becomes sore during treatment. Five of the 6 patients are alive and well. Two of these cases of cancer occurred in lateral aberrant thyroid tissue; one case occurred in a thyroglossal cyst. Growth continued normally in all with no evidence of myxœdema.

A. STANLEY KIRKLAND

The Use of Pentobarbital Sodium for Roentgen Nausea and Vomiting. Popp, W. C. and Binder, M. W., *Radiology*, 1937, 28: 211.

The cause of roentgen sickness being poorly understood, the authors began exhibiting a sedative at each treatment session; finally, pentobarbital was decided upon, because of its rapid sedative effect. Because most x-ray therapy cases are ambulatory, the taking of this drug by mouth was contraindicated at the time of treatment, because the patients were so influenced by the sedative that they could not be allowed to go home unattended. The drug was then administered in the form of a suppository, almost routinely, in doses of 3 grains—large doses caused too great a sedative effect. About 2 per cent of patients do not tolerate barbitur-

ates; of 175 who received pentobarbital during x-ray therapy, 61.1 per cent received complete relief from roentgen sickness, 18.3 had only moderate nausea, 16.9 per cent had nausea with slight vomiting, 9.7 had no relief. Pentobarbital is easily available, inexpensive, easily administered, and in the authors' experience, without harmful effects, and its use in controlling roentgen nausea is indicated.

A. STANLEY KIRKLAND

Anæsthesia

Cyclopropane Anæsthesia for Cæsarean Section: A Comparative Analysis of Two Hundred Cases. Morgan, G. S., Eaman, S. G. and Griffith, H. R., *Current Research in Anæsthesia & Anal.*, 1937, 16: 113.

The authors have made a comparative study of 100 cases of Cæsarean section performed under cyclopropane anæsthesia as compared with 100 cases in which the anæsthetic was mostly ethylene-ether combination. The results in general indicated that the post-operative course was smoother in those patients who had received cyclopropane. The question of vomiting and distension received particular consideration. Those patients receiving ethylene-ether in 7 cases showed severe distension which went on to paralytic ileus. In none of the cases receiving cyclopropane did this complication occur. There was no maternal death in the cyclopropane series. It was demonstrated that cyclopropane patients were out of bed in 14.3 days on the average, while the ethylene-ether group spent 17.4 days in bed. Thus it is evident that cyclopropane means an average of three days less hospitalization.

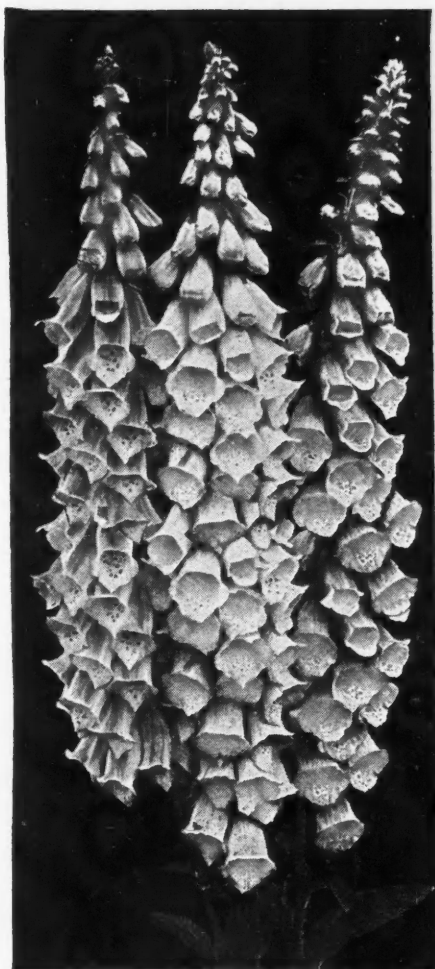
The authors are of the opinion that there is definitely less uterine hæmorrhage during cyclopropane anæsthesia, which would appear to be at variance with the generally accepted impression. However, they feel convinced that there is better uterine contraction under cyclopropane. Increased uterine tone sometimes makes the manual delivery of the baby quite difficult but the lessened hæmorrhage more than compensates for this.

F. ARTHUR H. WILKINSON

Hygiene and Public Health

The Cost of Tuberculosis to Industry, to the Individual, and to the Community. Sawyer, W. A. and Richard, E. K., *Am. Review Tuberculosis*, 1936, 33: 558.

The authors made a detailed study of all the costs involved in 100 cases of tuberculosis occurring in an industrial plant. There were 49 women and 51 men. Fifty-two of the cases were minimal A, 31 were moderately advanced, 14 were far advanced, and 3 were cases of tuberculous peritonitis. The costs ran from \$311 to \$24,508 in the minimal group; from \$612 to



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Literature on request

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\$15,889 in the moderately advanced group; and from \$114 to \$16,773 in the far advanced group. The case in this last group costing \$114 died, and no attempt is made to assess the cost to the community of the death.

FRANK G. PEDLEY

Occupational Cancer of the Lung. Teleky, L., *J. Indust. Hygiene & Toxicol.*, 1937, 19: 73.

Teleky is inclined to believe that chromate dust inhaled over a period of years may cause lung cancer. Modern chromate factories are much better managed than earlier ones and the workmen are less exposed to dust, so that the incidence of lung cancer among these workmen may be expected to decline.

The high incidence of lung cancer among the Schneeberg and Joachimsthal miners is notorious. Various explanations have been offered for this. Silica, nickel, cobalt and bismuth ores are found in these two mining districts, but it is unlikely that these metals themselves are causative agents since miners elsewhere do not appear to have a high incidence of lung cancer. Schneeberg and Joachimsthal miners certainly develop pulmonary fibrosis or silicosis, but there is no evidence to incriminate silicosis as a cause of cancer. Arsenic has been thought by some to be the causative agent but examination of the men does not indicate any great absorption of arsenic. The most probable explanation is radium or radium emanation. There is no doubt that the water in the region is quite strongly radio-active and examination of the air of the mines indicates the presence of radium emanation. Examination of the miners themselves for radium so far has not been conclusive.

FRANK G. PEDLEY

Experimental Investigation of "Aniline Cancer". Berenblum, I. and Bonser, G. M., *J. Indust. Hygiene & Toxicol.*, 1937, 19: 86.

The prevalence of bladder cancer among workers in the aniline dye industry is now an accepted fact. Aniline benzidine, and α and β naphthylamine appear to be the most frequently implicated substances.

The author has endeavoured to produce bladder tumours in rabbits by intraperitoneal injection of these substances. Some of the rabbits survived the injections for as long as 4 years. None were found to have bladder tumours. Feeding and inhalation experiments were performed on rats with similar negative results. Finally the urine of workmen in a dye factory in which cases of aniline cancer had previously been reported was extracted with ether or chloroform, and the extract was painted on the skin of mice—no tumours appeared. The literature on the subject is discussed.

FRANK G. PEDLEY

Obituaries

Dr. George Alexander MacCallum*

AN APPRECIATION

Dr. George Alexander MacCallum died suddenly at Baltimore, Md., on September 30, 1936, at the age of ninety-three. The son of George MacCallum, who had emigrated from Scotland in 1840, and Jane Sangster (the sister of the great schoolmaster, John Sangster, M.D., 1831-1904), he was born at Toronto on April 23, 1843. The family moved to Stouffville, north of Toronto in 1845, and there ten other children were born. One of these, John Sangster, became a doctor and practised at Smith's Falls, where he died in 1935, aged eighty-eight.

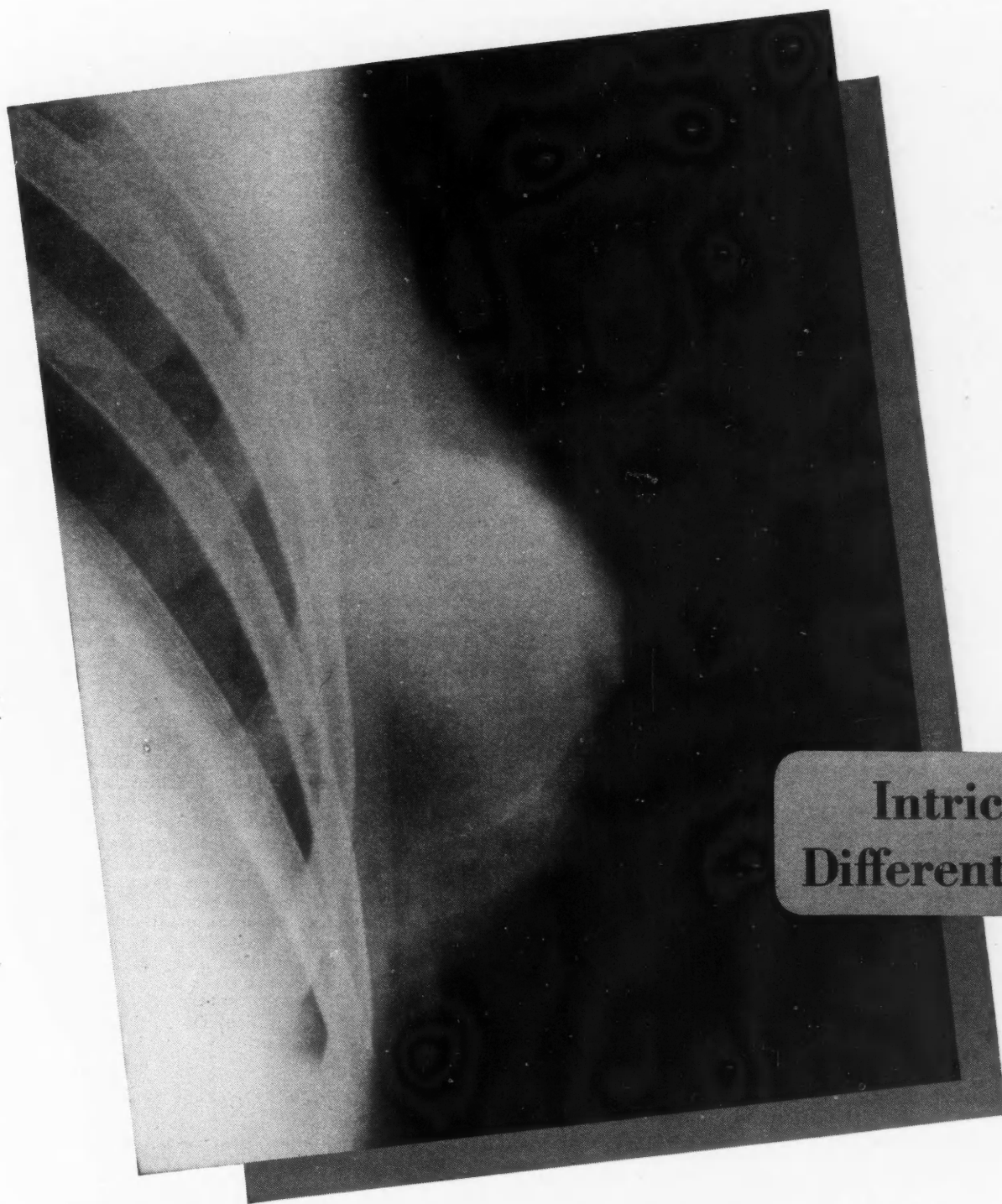
Dr. MacCallum had to work hard on the land when he was a youth, for money was scarce, and when he was sixteen began to teach school at Ringwood. His ambition was to enter the medical profession and whilst tutoring the son of their family doctor, Andrew Lloyd, he helped the latter in his surgery and even visited patients when the doctor was away. He became a student in the Medical Department of Victoria University, Toronto, and, after two sessions of six months each, graduated M.D. in 1866. He entered into practice at Whitevale and later at Sanford, but when he had saved enough money he moved to Dunnville on the Grand River in January, 1868.

Dr. MacCallum remained there, engaged in an extensive practice, until 1902. In 1870 he married Florence Octavia Eakins, of Sparta, Ont. They had two sons and two daughters: William George, who is Professor of Pathology at Johns Hopkins University, succeeding the late William H. Welch; John Bruce, a very distinguished embryologist and physiologist, who died at Berkeley, California, in 1906 at the age of twenty-nine; Bertha Alexandra, who died in 1923; and Marion Josephine, who is the wife of Professor Herbert W. Rand, of the Department of Zoology at Harvard University.

At Dunnville, Dr. MacCallum's life was that of a country doctor, especially interested in surgery, who drove far and wide to visit his patients or to operate upon them in their homes. So busy was he that his two horses were often overworked with long drives. In addition to all this, Dr. MacCallum was an ardent naturalist, archæologist, and hunter of woodcock, quail, and ruffed grouse. There was nothing in Nature in which he did not have a scientific interest, and his letters to my father, Dr. Archibald E. Malloch, of Hamilton, written every two weeks or so for a couple of score of years, always contained references to plants, birds, or animals that he had seen, or criticisms of articles he had read in such publications as *Forest and Stream*. His enthusiasm was infectious and little wonder was it that his two sons were so eminently successful in their scientific careers. His house at Dunnville was truly a museum and contained a large collection of stuffed birds and Indian relics of all kinds. This collection is now at Queen's University. Every autumn he was joined on some of his shooting expeditions by Dr. Malloch; they were both devoted to their dogs.

Dr. MacCallum was an energetic Liberal in politics and in 1882, and again in 1887, was a candidate for the Dominion House, but was defeated on both occasions. He was eagerly interested in the preservation of fish and game, and in 1890 was appointed by the Ontario Government on a Commission "To enquire into and report upon the game and fish of the Province of Ontario and the laws relating thereto". In 1892

* Taken very largely from the authoritative biographical sketch which appeared in the *Dunnville Weekly Chronicle*, December 25, 1936.



Intricate Differentiation

A WOMAN patient complains of pain or swelling in the breast, with other minor clinical symptoms. Is it chronic mastitis...cystic mastitis...tumor...abscess...hematoma...developing fibrosis...early carcinoma? The physician is confronted with a difficult problem in such a situation. A diagnosis based on clinical signs alone

may lead to mistaken conclusions.

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RADIOGRAPHS PROVIDE DIAGNOSTIC FACTS

this Commission issued a thick volume containing a discussion of the state of the regulations and suggestions for new laws. As Chairman, Dr. MacCallum contributed a description of the birds of Ontario illustrated by drawings and photographs of his own specimens. From 1893 to 1902 he was Chairman of the permanent Fish and Game Commission. The splendid laws suggested by this Commission were adopted by Ontario, other provinces, and served as models for those of several of the United States. In 1905, the North America Fish and Game Protective Association was organized, and Dr. MacCallum was elected Chairman. In 1902 he was offered and accepted the position of Superintendent of the Asylum at London, Ont. So he gave up his arduous practice and moved to London where, besides reorganizing and rebuilding the Asylum, he lectured on psychiatry at the University of Western Ontario. In 1908 he was transferred to Penetanguishene, where he remained until 1910, when he resigned, and with his family moved to New York to be near his elder son who was Professor of Pathology at Columbia University. Although he was then sixty-seven years of age, he was very active and undertook the study of worm parasites, working during the summer at Woods Hole and during the rest of the year for the New York Zoological Society at the Bronx Zoological Park and the New York Aquarium, to both of which he was appointed Pathologist. The results of his studies are embodied in a large number of papers in American and foreign scientific publications. He gave his extensive collection of parasites to the United States National Museum at Washington.

In 1921 Dr. MacCallum moved to Baltimore where his son had been appointed Professor of Pathology at the Johns Hopkins University. His wife died in 1931, and in 1933, when he was ninety years of age, his health became poor.

Dr. MacCallum was a man of splendid appearance and carriage, and was endowed with great physical strength, which perhaps enabled him, when old, to survive several very serious illnesses. He was a man of whom the profession of Canada and the United States is justly proud.

ARCHIBALD MALLOCH

Dr. James Vickers Anglin, of Saint John, N.B., died on July 8, 1937, in his seventy-seventh year. He was born in Kingston, Ont., and a graduate of Queen's University (1887).

In 1891, he joined the staff of the Verdun Protestant Hospital, Verdun, Que., where he was assistant medical superintendent. In 1904, he was appointed head of the Provincial Hospital for Nervous Diseases at Lancaster, a suburb of Saint John, serving in that capacity for thirty years until retirement. In 1918 he was President of the American Psychiatric Association.

Dr. Andrew Bradford.—After completing almost half a century in the practice of medicine, Dr. Andrew Bradford, of Sexsmith, Alta., died recently. He graduated in 1887 from Trinity Medical College, Toronto, and practised in the East for thirty years, during which time he went to Edinburgh for post-graduate work, returning with L.R.C.S. and M.R.C.S. diplomas. Twenty years ago he heard the call of the West, and came to Alberta, where he had remained for two decades.

Dr. Bradford was a man of fine qualities and rendered good service to the people in the pioneer districts, until he retired to spend the sunset of his life on his farm, where he quietly passed away just before Christmas, 1936. He leaves a widow, a daughter and one son. Dr. A. C. Bradford, of Edmonton, to mourn his loss.

Dr. Arthur Valentine Brown, of Kitchener, Ont., died on June 21, 1937. He was born in 1881 and a graduate of Trinity University, Toronto (1904).

Dr. George Buchanan, of Toronto, Ont., a pioneer medical doctor in Zurich, Ont., for 35 years, died on June 14, 1937. He was ninety-four years of age and had been retired for 30 years, during which time he had been a resident in Toronto. Born in Scotland, Dr. Buchanan received his medical degree from the University of Toronto (1871), and after graduation established a practice in Zurich. His wife died 24 years ago. Surviving are three sons, George, of Sudbury, Prof. Milton Buchanan, of the University of Toronto, and Dr. Norman Buchanan, of Peterborough; and two daughters, Clara and Pearl, at home.

Dr. William Thomas Burns, of Toronto, Ont., died on June 3, 1937, in his sixty-fourth year. He was a graduate of the University of Toronto (1900), and retired from active practice in 1925.

Dr. Walter Livingston Coulthard, of Vancouver, B.C., died recently from a heart attack. He was born in Valleyfield, Que., and was educated at the University of Toronto, taking both Arts and Medicine. He graduated M.B. in 1894. After graduation he practised for several years in Toronto, then went to British Columbia to practise. In 1904 he entered Harvard University for post-graduate work and later went to the Polyclinic Hospital, New York. He had been in active practice in Vancouver since 1905.

Dr. Charles Schomberg Elliott, of Halifax, N.S., died on June 1, 1937. He was born in Stillwater, in 1864, the son of the late Henry Elliot and Mrs. Elliot, and a grandson of the late Dr. Henry Elliot, first lieutenant in the Royal Marines.

His early education was received at Pictou Academy and Dalhousie University. He graduated from Bellevue Medical College, New York, in 1891. Dr. Elliot's first practice was in Guysboro town, and there he was married to Miss Minnie Selden in 1897. In 1901 he went to Stellarton, where he practised for a number of years, later coming to Halifax, where he was first connected with the Canadian Army Medical Corps. He had practised in Halifax since the war.

Dr. James L. Gibson, of Lynden, Ont., died on June 10, 1937. He was a graduate of Queen's University (1893).

Dr. George Gordon, of Newbury, Ont., died on May 30, 1937, at the residence of his daughter, Mrs. Edward McAuley. He was eighty-two years old and a graduate of the University of Toronto (1867).

Dr. Frederick Samuel Harper, of Hamilton, Ont., died on June 15, 1937. He was born in 1887 and a graduate of the University of Toronto (1910).

Dr. L. L. Harrison, of Halifax, N.S., died suddenly on June 20th, after he had performed a minor operation at the home of a patient. He was in the act of drying his instruments when he suddenly collapsed. He was a graduate of McGill (1904).

Dr. Herbert Maw, Caledonia, Ont., died on May 26, 1937. He apparently collapsed after an accident in which his motor car was ditched. He was a graduate of Trinity University (1897).

Dr. W. A. McCauley.—One of the great figures of Northern Ontario's mining area was lost to the Dominion in the death of Dr. W. A. McCauley on June 6th. The veteran physician was drowned while swimming off his island cottage on Lake Penage little



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more than a month after he had retired as chief of medical staff for the International Nickel Company of Canada Limited.

During his 32 years on the medical staff of the company Dr. McCauley was responsible for a number of innovations in the care of mining men in Northern Ontario as well as for the development of the medical facilities at Copper Cliff Hospital, of which he was superintendent for 26 years.

A graduate of the University of Toronto (1902), Dr. McCauley was on the staff of the Toronto General Hospital until 1905, when he went to Copper Cliff as company surgeon. In 1911 he was appointed superintendent of the Copper Cliff Hospital, a post he held until his retirement May 31, 1937.

Dr. McCauley's reputation as a medical man extended beyond Northern Ontario to all sections of the profession. He was a pioneer in the development of modern methods, not only in the mining industry but in medical care of lonely settlers and sportsmen in the North. X-ray files of the Copper Cliff Hospital illustrate his skill and resourcefulness. One photo, taken more than 20 years ago, shows the right hip of Alex. Pakkala. As a boy of six years, Alex. was partially buried in a sand pit cave-in and suffered a compound fracture of his hip. Treating it by internal fixation, Dr. McCauley cleverly repaired the fracture with a steel pin, which the x-ray photo clearly shows in its place. Today Alex. is an International Nickel Company employee, doing his full day's work in Copper Cliff Smelter. He has always had 100 per cent function of the fractured member since it was treated. Only in the recent years has the method then devised by Dr. McCauley become standard in the medical profession.

Dr. Thomas Wellesley Peart, of Hamilton, Ont., died on June 4, 1937. He was born in 1888, the son of the late Arthur W. Peart and Mrs. Peart, of Saint John, N.B. He was a graduate of the University of Toronto (1909).

Dr. James Wason Smylie, of Mine Center, Ont., died by drowning recently. He was born at Camborn, near Cobourg, Ont., 51 years ago, where he obtained his public school education. When fourteen years old he went to the United States, where he put himself through university, graduating as an M.D., and a D.Sc., and earned a post-graduate course at Harvard. He practised medicine in Colorado Springs and in Northern Ontario before he entered the field of mineralogy, which occupied his talents from 1924 to the time of his death.

Dr. Gordon Edward Stanley. One of Alberta's young physicians, in the person of Dr. Stanley, died on May 24th at Hazelton, British Columbia, where he was assisting Dr. L. B. Wrinch. It seems tragic when a very popular and capable young physician passes away at the commencement of his career.

THE DOCTOR'S EPITAPH

The doctor sleeps! No more at pain's behest
Shall he relinquish his much needed rest;
No more his skilful hand and kindly heart
Shall give to some new life a proper start.
The doctor sleeps! His fighting days are done
But hundreds live because of bouts he won,
And, generations hence, those will draw breath
Who would not be had he not conquered death.
The doctor sleeps! Might we his deeds recall,
His name would blaze in fame's enmarbled hall.
But serving modestly through life, it now seems best
Merely to write, "His work survives, and let him rest".

—Anonymous.

News Items

Alberta

A committee composed of representatives of the Pharmaceutical Association and the medical profession met in Edmonton recently, on the invitation of the pharmacists, to discuss the question of the adoption of the formulary which would be the basis on which drugs would be dispensed and prescriptions filled. It is claimed that if such were adopted that prescriptions would cost less to the patient and the pharmacist could carry fewer preparations in stock. A committee has been appointed to give the details very careful consideration, to report back to their respective associations for sanction.

The College of Physicians and Surgeons of Alberta offers annually to the students in medicine of the Provincial University five cash scholarships of \$50.00 each. It is noted from the list of those who received the scholarships that two out of five were won by women, which is quite out of proportion to the number of women enrolled.

At the recent session of the Alberta Legislature an amendment to the Workmen's Compensation Act was passed permitting the appointment of a Board of Review consisting of forty medical men, twenty of whom to be appointed from the northern portion of the province and twenty from the south. From this group smaller boards will be chosen to review compensation cases, with a view of having a finality, so that the case once closed will not be reopened. It is thought that by the appointment of the larger board specialists in every phase of the case will be thus available, resulting in equitable decisions.

The Alberta Legislature has appointed a Commission of its members to review the Workmen's Compensation Board under the Act, to hear representations and receive suggestions from any or all interested parties and thus make a report to the Legislature with a view to revising the Act. Any individual or body presenting matters for consideration is required to furnish twelve copies. The College of Physicians and Surgeons is calling on its members to report in the matter.

The Province of Alberta has accommodation at the present time for 2,280 patients in the following institutions: Ponoka Mental Hospital, 1,490; Oliver Mental Hospital, 476; Claresholm Mental Hospital, 100; Red Deer Training Institute, 214.

Owing to the fact that the tendency to hospitalize mental patients is increasing, the Alberta Government has announced its intention to build an extension to the Oliver institution, thus adding 250 additional beds.

Owing to climatic conditions and an active campaign in following up contacts, as well as to increased hospitalization during the last decade the death rate from tuberculosis has been reduced from 60 to 43 per 100,000 population.

Carmangay has recently opened up a new hospital and Notikwin, Rocky Mountain House, and Claresholm are actively engaged in new hospital projects.

The Calgary City Health Officer, Dr. W. H. Hill, has sounded a warning concerning the bubonic plague, which has been making considerable headway in the western section of the United States. He has warned the people against feeling satisfied that Canada might be immune.

G. E. LEARMONTH

Protecting Children . . .

Now that schools are about to re-open, physicians are again reminding parents to have their children given the benefit of specific protection against certain communicable diseases. This protection is highly important both for school children and for younger children and infants.

Diphtheria

The administration of three doses of diphtheria toxoid has been found to be most effective in affording protection against diphtheria. Active immunity to this disease is established in well over ninety per cent of those receiving the three injections.

Smallpox

Modern technique and vaccine virus of assured potency make possible a maximum number of "takes" with a minimum of reactions and scars.

Scarlet Fever

Protection as evidenced by the Dick Test can be demonstrated in the case of more than seventy per cent of children following their receiving five doses of scarlet fever streptococcus toxin.

Whooping Cough

Injections of a vaccine made from freshly isolated strains of *H. pertussis* have given most promising results in prevention of whooping cough. This disease provides an outstanding illustration of the importance of immunizing children before their attaining of school age. Often, as in the case of whooping cough, it is among the younger children and infants that illness, sequelae and death occasioned by communicable diseases are most notable.

CONNAUGHT LABORATORIES
UNIVERSITY OF TORONTO
TORONTO 5 - - CANADA

British Columbia

The Royal Columbian Hospital, New Westminster, held "open house" on June 17th to 19th in celebration of its seventy-fifth anniversary.

Hon. G. S. Pearson, Minister of Mines, has stated that much interest is being shown in British Columbia over the recent reported discovery by the Banting Institute of some means of partial control over silicosis. The Workmen's Compensation Board is considering setting up a special committee to investigate means of controlling or preventing silicosis, and mining operators have already set up a voluntary organization with the same objective.

Mr. Henry M. Grant, Director of the Family Relations Bureau of San Francisco, has come to Vancouver under the auspices of the Greater Vancouver Health League to lecture to various organizations on the objects of sex education, prevention of venereal disease, birth control and cognate subjects. He has opened a sex education institute in the auditorium of the Vancouver General Hospital.

The health insurance plebiscite held simultaneously with the provincial general election on June 1st showed in returns from 38 out of 40 ridings that a majority of about 35,000 had been secured in its favour. The situation which forced the government to seek a plebiscite has not changed however. The medical opposition to the scheme proposed has not altered, and the differences of opinion which threatened to split the cabinet last year still exist.

D. E. H. CLEVELAND

Manitoba

The appointment is announced of Miss Catherine Lynch as Superintendent of Nurses and Principal of the School of Nursing of the Winnipeg General Hospital.

Miss Lynch, who is at present superintendent of nurses at the Provincial Mental Hospital, Ponoka, Alta., was born in Manitoba, is a graduate of the Winnipeg General Hospital, class of 1925, with subsequent post-graduate work in New York, and recently at the School of Graduate Nurses, McGill University. Miss Lynch will take over her new duties on September 1st.

ROSS MITCHELL

New Brunswick

Dr. E. W. Lunney, Senior Anæsthetist at the Saint John General Hospital, has recently been elected President of the American Association of Anæsthetists.

Preparations for Militia Camp at Sussex, N.B., are now complete, and No. 14 Field Ambulance under the command of Col. V. D. Davidson will attend camp with a larger complement of officers than for many years past. Medical arrangements are in the hands of Lt.-Col. R. A. Hughes, D.M.O.

Dr. R. J. Collins, Superintendent of the Saint John Tuberculosis Hospital, has recently been elected President of the Canadian Tuberculosis Association. Dr. Collins has just returned home from an extended tour of Europe, where his attention was devoted to advance in the treatment of tuberculosis.

Dr. A. L. Winsor, of Norton, was recently honoured by his colleagues of the Saint John Medical Society at a complimentary dinner, to celebrate his approaching marriage.

A very large number of physicians from New Brunswick attended the Annual Meeting of the Cana-

dian Medical Association in Ottawa, the delegation being representative of all parts of the province.

Hon. Dr. W. F. Roberts, Minister of Health, has returned home in improved health, following an operation at the Royal Victoria Hospital, Montreal.

It is reported that Dr. E. W. Rowley, who has been confined to the hospital for several months suffering from cardiac disease, has returned home, showing definite improvement.

A. STANLEY KIRKLAND

Nova Scotia

Dr. Kenneth MacKenzie, of Halifax, has been named President-elect of the Canadian Medical Association for 1938-39. The meeting of the Association for 1938 will take place in Halifax. Dr. J. R. Corston, of Halifax, was elected a member of the Council.

The new tuberculosis annex to the Highland View Hospital at Amherst will be constructed at a cost of \$17,000. The council of the hospital announced that the Provincial Government had advanced \$1,500 towards the cost of construction.

Dr. Victor Mader, of Halifax, was re-elected Vice-president of the Maritime Zone of Canadian Flying Clubs Association at the annual meeting in Regina.

Dr. A. J. MacDonald, of Wickford, Rhode Island, who has been in the United States for the past thirty years died on June 11th. He was a native of Iron Ore, Pictou County.

The provincial election saw several members of the medical profession victorious at the polls. Hon. Dr. F. R. Davis, Minister of Health, was returned for Lunenburg County. Dr. J. L. MacIsaac for Antigonish, Dr. W. D. Forrest, head of the City Department of Health, was returned for a Halifax riding, and Dr. M. E. McGarry for Inverness. Dr. H. B. Havey was an unsuccessful candidate in Colchester County.

Dr. J. Howard Mueller, Associate Professor of Bacteriology at Harvard University, is at present a visitor to Dalhousie University, where he is continuing his researches on the metabolism of bacteria.

N. B. DREYER

Ontario

A. D. Lapp, M.D., D.P.H., for fifteen years in charge of the Sanitarium at Tranquille, B.C., has been appointed Superintendent of the new St. Lawrence Tuberculosis Sanitarium at Cornwall.

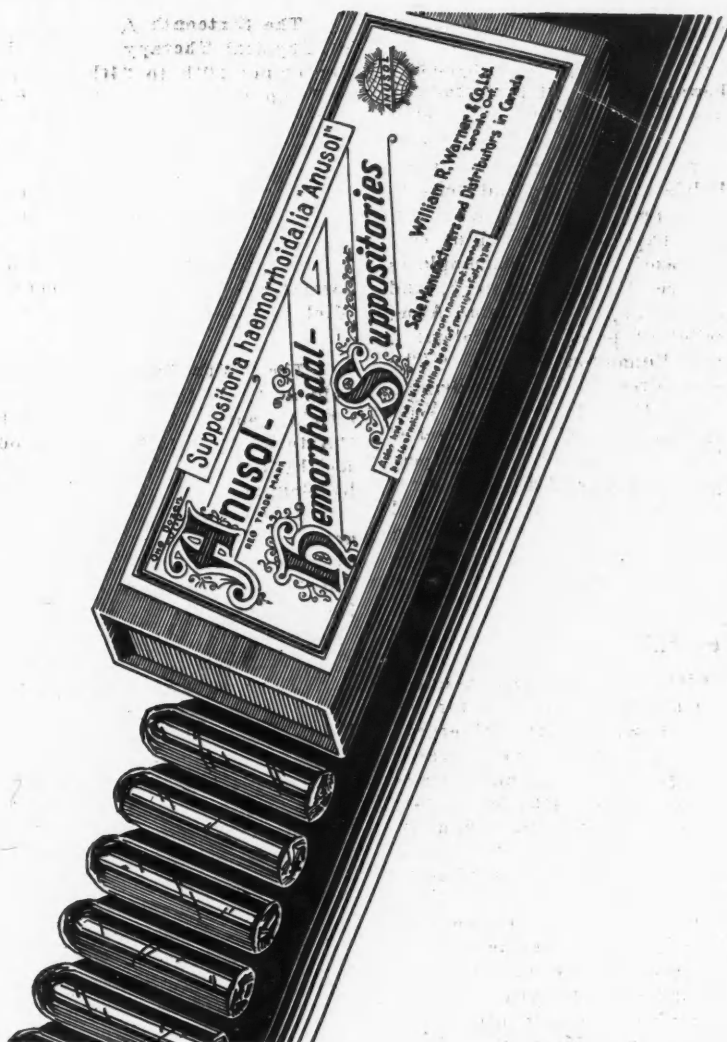
Drs. G. K. Kitchen and H. R. C. Norman, of Toronto, have passed their primary Fellowship examination in the Royal College of Surgeons of England.

On June 15th, the Hawk Junction Red Cross Hospital was formally opened, to meet the needs of the Michipicoten mining area, a district of some 24,000 square miles. The building has been erected by local enterprise and will be staffed and maintained by the Ontario Red Cross.

Dr. R. E. Mitchell, of the Sarnia General Hospital, has been appointed Hospital Radiologist in New Westminster, B.C.

The Niagara Peninsula Sanitarium at St. Catharines is considering tenders for the construction of a nurses' residence.

J. H. ELLIOTT



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Saskatchewan

Under the auspices of the College of Physicians and Surgeons of Saskatchewan, a series of post-graduate lectures was given at the District Medical Societies during the month of June as follows. Moose Jaw, Swift Current and Rosetown.—Dr. A. J. Fisher, of Calgary, Alta., gave papers on "Pelvic architecture and delivery prognosis", and "Eclampsia and pre-eclampsia". Dr. E. P. Scarlett, Calgary, gave papers on "Changing conceptions of biliary tract disease", and "Commonplaces of medical practice". Prince Albert, Saskatoon, and North Battleford.—Dr. L. C. Conn, of Edmonton, Alta., gave a paper on "The relief of pain during labour", and Dr. D. B. Leitch, of Edmonton, one on "The significance of vomiting in children". Yorkton, Regina, Weyburn and Broadview.—Dr. C. E. Corrigan, of Winnipeg, gave a paper on "Appendicectomy without relief of symptoms", and Dr. C. W. MacCharles, of Winnipeg, one on "Some recent advances in diagnosis and treatment in gynaecology". All the meetings were well attended and the tours proved a success, especially in view of the practicality of the subject matter in the papers presented.

LILLIAN CHASE

General

The Pan-American Medical Association announces that the *Queen of Bermuda* has been chartered for the Seventh Cruise-Congress. Following is the itinerary: leave New York, January 15, 1938; arrive Havana, 18th (4½ days and 5 nights in Havana); leave Havana, 23rd; arrive Port au Prince, 24th; leave Port au Prince, 24th; arrive Trujillo City (Santo Domingo), 26th; leave Trujillo City (San Domingo), 26th; arrive San Juan (Puerto Rico), 27th; leave San Juan (Puerto Rico), 27th; arrive New York, 31st.

The main part of the Congress will be held in Havana. There will be three days of scientific sessions with operative clinics. These will be divided into sections for the various specialties. This year we have four new sections: tuberculosis; gastroenterology; dentistry; and industrial medicine. Meetings will be arranged with our medical colleagues at the other ports of call.

The Hotel Savoy-Plaza in New York and the National Hotel in Havana will be the official hotels.

Travelways, Inc., have chartered the *Queen of Bermuda* on behalf of our Association and will act as our official travel agents. As this Congress promises to be the most successful ever held by the Association, it would be highly advisable to book reservations as early as possible with Travelways, Inc., who will make every effort to satisfy the requirements of the members of the Congress. Applications for reservations should be addressed to the Pan-American Medical Association at 745 Fifth Avenue, New York City.

The program committee would be pleased to receive applications for the presentation of scientific contributions. Dr. Joseph J. Eller, Director-General, 745 Fifth Ave., New York City.

The National Organization for Public Health Nursing will meet with the American Public Health Association in 1937 for the first time. This large and important organization is expected to add another thousand to the registration lists.

The following related societies will meet with the Association as usual: The American Association of School Physicians; International Society of Medical Health Officers; Conference of State Sanitary Engineers; Conference of State Laboratory Directors; Association of Women in Public Health; Delta Omega.

Dr. Reginald M. Atwater is the Executive Secretary of the Association, and the headquarters' offices are at 50 West 50th Street, New York, N.Y.

The Sixteenth Annual Session, American Congress of Physical Therapy, will be held in Cincinnati from September 20th to 24th.—From every standpoint this 16th annual session offers an intensive "refresher" course, in which will be embraced subjects like short wave diathermy, ultra-violet radiation, low voltage currents, exercise, massage, etc. Featured symposia include fractures, vascular diseases, poliomyelitis, fever therapy. There will be no registration fee, but the meeting is open only to duly licensed physicians and properly vouched for technical assistants. For information address the Executive Director, 30 North Michigan Ave., Chicago, Ill.

The XVth Concilium Ophthalmologicum is to be held at Cairo from December 8 to 14, 1937. The two official subjects of the conference will be: (1) "Arterial hypertension", introduced by Wagener and Keith; (2) "Endocrinology of the eye", introduced by Snapper.

A scientific and commercial exhibition have been arranged. Subscription for membership is open to every medical man at a charge of 50 Swiss Francs. The General Secretary is Dr. Mohamed Tewfik, P.O.B. No. 2001, Cairo, Egypt.

Book Reviews

British Encyclopædia of Medical Practice. Vol. 3. Edited by Sir Humphry Rolleston, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D. 681 pages. \$10.00 a vol. Butterworth, Toronto, 1937.

This volume continues the series in the same form, and includes subjects from "Cataract" to "Diaphragm Diseases". There are also many references to other headings. "Catarrh" for instance is referred to "Accessory Sinuses of the Nose", "Bronchitis" and "Colds". One admires again the compression into small space of such a subject as "Cellulitis", in which one notes admirable conservatism in treatment; in "Cerebrospinal Fluid", where Dr. Greenfield sets forth the essentials of the subject most clearly and sufficiently; in "Cranial Nerve Affections" by Dr. F. M. B. Walshe. Also one cannot but comment on the degree to which the encyclopædia is brought up to date, for example, in the chapter on "Diabetes Mellitus" in which one finds full reference to Canadian workers' development of protamine zinc insulin, which must have appeared when the book was practically completed. The illustrations, as before noted, are good, much reliance wisely being placed on line drawings; but there are also some excellent coloured plates especially in connection with conjunctivitis and cataract.

Buchanan's Manual of Anatomy. Edited by J. E. Frazer, D.Sc., F.R.C.S., Professor of Anatomy, University of London. Sixth ed., 1772 pages. Price \$10.50. Macmillan Co., Toronto, 1937.

This is the sixth edition of a standard manual of anatomy. The old English nomenclature has been replaced by the new Birmingham revision. It is a good, clearly written anatomy.

The Home Treatment of Spastic Paralysis. P. M. Girard, M.D., F.A.C.S., Chief of Orthopaedic Service, Parkland Hospital, Texas. 130 pages, illustrated. Price \$2.25. J. B. Lippincott, Philadelphia, London and Montreal, 1937.

A pleasantly written and well illustrated manual of training for the sadly handicapped spastic paralytics.

